

**Clinical trial results:****A Phase 2b/3 Multicenter, Randomized, Double-Masked, Dose-Ranging Study Comparing the Efficacy and Safety of Emixustat Hydrochloride (ACU-4429) with Placebo for the Treatment of Geographic Atrophy Associated with Dry Age-Related Macular Degeneration****Summary**

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2012-004952-12 |
| Trial protocol           | DE             |
| Global end of trial date | 15 April 2016  |

**Results information**

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v1 (current)      |
| This version publication date  | 18 September 2021 |
| First version publication date | 18 September 2021 |

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

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 4429-202 |
|-----------------------|----------|

**Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01802866 |
| WHO universal trial number (UTN)   | -           |

Notes:

**Sponsors**

|                              |                                                                                                   |
|------------------------------|---------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Acucela Inc.                                                                                      |
| Sponsor organisation address | 600 University Street, Suite 2900, Seattle, United States, 98101                                  |
| Public contact               | Acucela Clinical Trials Helpdesk, Acucela Inc., +1 2068058310, clinicaltrials@acucela.com         |
| Scientific contact           | Acucela Clinical Trials Helpdesk, Acucela Inc., 2068058300 2068058310, clinicaltrials@acucela.com |

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

|                                                      |               |
|------------------------------------------------------|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 15 April 2016 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 15 April 2016 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 15 April 2016 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

To determine if ACU-4429 reduces the rate of progression of geographic atrophy (GA) compared to placebo in subjects with dry age-related macular degeneration (AMD).

Protection of trial subjects:

All subjects were required to read and sign an informed consent form.

Background therapy: -

Evidence for comparator: -

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment                          | 18 January 2013 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Germany: 57        |
| Country: Number of subjects enrolled | United States: 451 |
| Worldwide total number of subjects   | 508                |
| EEA total number of subjects         | 57                 |

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)                      | 28  |
| From 65 to 84 years                       | 382 |
| 85 years and over                         | 98  |

## Subject disposition

### Recruitment

Recruitment details:

A total of 503 subjects were randomized and received study drug at 49 sites in the United States and 7 sites in Germany from February 2013 to April 2016.

### Pre-assignment

Screening details:

A total of 968 subjects were screened, and 508 subjects were randomized. The most common reason for failing screening was the total area of GA not meeting an inclusion criterion (n = 219/460 screen failures).

### Period 1

|                              |                                                               |
|------------------------------|---------------------------------------------------------------|
| Period 1 title               | Overall Trial (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>             | Emixustat 2.5 mg |

Arm description:

Subjects took one oral tablet of emixustat 2.5 mg per day for 24 months.

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

Dosage and administration details:

Emixustat 2.5 mg oral tablet taken once daily

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Emixustat 5 mg |
|------------------|----------------|

Arm description:

Subjects took one oral tablet of emixustat 5 mg per day for 24 months.

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

Dosage and administration details:

Emixustat 5 mg oral tablet taken once daily

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | Emixustat 10 mg |
|------------------|-----------------|

Arm description:

Subjects took one oral tablet of emixustat 5 mg per day for 1 month, then one oral tablet of emixustat 7.5 mg per day for 1 month, and then one oral tablet of emixustat 10 mg per day for 22 months.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

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

Dosage and administration details:

One oral tablet of emixustat 5 mg per day for 1 month, then one oral tablet of emixustat 7.5 mg per day for 1 month, and then one oral tablet of emixustat 10 mg per day for 22 months.

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

Arm description:

Subjects took one oral tablet of placebo per day for 24 months.

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

Dosage and administration details:

1 tablet taken by mouth each day

| <b>Number of subjects in period 1</b>           | Emixustat 2.5 mg | Emixustat 5 mg | Emixustat 10 mg |
|-------------------------------------------------|------------------|----------------|-----------------|
| Started                                         | 134              | 135            | 103             |
| Completed                                       | 78               | 81             | 53              |
| Not completed                                   | 56               | 54             | 50              |
| Adverse event, serious fatal                    | 3                | 2              | 1               |
| Physician decision                              | 1                | -              | -               |
| Consent withdrawn by subject                    | 16               | 8              | 9               |
| Randomized in error, did not receive study drug | 1                | -              | -               |
| Adverse event, non-fatal                        | 33               | 44             | 39              |
| Lost to follow-up                               | 2                | -              | 1               |

| <b>Number of subjects in period 1</b>           | Placebo |
|-------------------------------------------------|---------|
| Started                                         | 136     |
| Completed                                       | 108     |
| Not completed                                   | 28      |
| Adverse event, serious fatal                    | -       |
| Physician decision                              | 2       |
| Consent withdrawn by subject                    | 6       |
| Randomized in error, did not receive study drug | 3       |
| Adverse event, non-fatal                        | 15      |
| Lost to follow-up                               | 2       |



## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                       |                  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| Reporting group title                                                                                                                                                                                 | Emixustat 2.5 mg |
| Reporting group description:                                                                                                                                                                          |                  |
| Subjects took one oral tablet of emixustat 2.5 mg per day for 24 months.                                                                                                                              |                  |
| Reporting group title                                                                                                                                                                                 | Emixustat 5 mg   |
| Reporting group description:                                                                                                                                                                          |                  |
| Subjects took one oral tablet of emixustat 5 mg per day for 24 months.                                                                                                                                |                  |
| Reporting group title                                                                                                                                                                                 | Emixustat 10 mg  |
| Reporting group description:                                                                                                                                                                          |                  |
| Subjects took one oral tablet of emixustat 5 mg per day for 1 month, then one oral tablet of emixustat 7.5 mg per day for 1 month, and then one oral tablet of emixustat 10 mg per day for 22 months. |                  |
| Reporting group title                                                                                                                                                                                 | Placebo          |
| Reporting group description:                                                                                                                                                                          |                  |
| Subjects took one oral tablet of placebo per day for 24 months.                                                                                                                                       |                  |

| Reporting group values                                                                                                                                                                                                                                    | Emixustat 2.5 mg | Emixustat 5 mg | Emixustat 10 mg |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|----------------|-----------------|
| Number of subjects                                                                                                                                                                                                                                        | 134              | 135            | 103             |
| Age categorical<br>Units: Subjects                                                                                                                                                                                                                        |                  |                |                 |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                  |                |                 |
| Age continuous<br>Units: years                                                                                                                                                                                                                            |                  |                |                 |
| arithmetic mean                                                                                                                                                                                                                                           | 78.2             | 78.2           | 77.2            |
| standard deviation                                                                                                                                                                                                                                        | ± 7.11           | ± 7.79         | ± 7.96          |
| Gender categorical<br>Units: Subjects                                                                                                                                                                                                                     |                  |                |                 |
| Female                                                                                                                                                                                                                                                    | 79               | 73             | 61              |
| Male                                                                                                                                                                                                                                                      | 55               | 62             | 42              |

| Reporting group values                                                                 | Placebo | Total       |  |
|----------------------------------------------------------------------------------------|---------|-------------|--|
| Number of subjects                                                                     | 136     | 508         |  |
| Age categorical<br>Units: Subjects                                                     |         |             |  |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days) |         | 0<br>0<br>0 |  |

|                                          |        |     |  |
|------------------------------------------|--------|-----|--|
| Infants and toddlers (28 days-23 months) |        | 0   |  |
| Children (2-11 years)                    |        | 0   |  |
| Adolescents (12-17 years)                |        | 0   |  |
| Adults (18-64 years)                     |        | 0   |  |
| From 65-84 years                         |        | 0   |  |
| 85 years and over                        |        | 0   |  |
| Age continuous                           |        |     |  |
| Units: years                             |        |     |  |
| arithmetic mean                          | 77.1   |     |  |
| standard deviation                       | ± 8.13 | -   |  |
| Gender categorical                       |        |     |  |
| Units: Subjects                          |        |     |  |
| Female                                   | 77     | 290 |  |
| Male                                     | 59     | 218 |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                       |                  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| Reporting group title                                                                                                                                                                                                                 | Emixustat 2.5 mg |
| Reporting group description:<br>Subjects took one oral tablet of emixustat 2.5 mg per day for 24 months.                                                                                                                              |                  |
| Reporting group title                                                                                                                                                                                                                 | Emixustat 5 mg   |
| Reporting group description:<br>Subjects took one oral tablet of emixustat 5 mg per day for 24 months.                                                                                                                                |                  |
| Reporting group title                                                                                                                                                                                                                 | Emixustat 10 mg  |
| Reporting group description:<br>Subjects took one oral tablet of emixustat 5 mg per day for 1 month, then one oral tablet of emixustat 7.5 mg per day for 1 month, and then one oral tablet of emixustat 10 mg per day for 22 months. |                  |
| Reporting group title                                                                                                                                                                                                                 | Placebo          |
| Reporting group description:<br>Subjects took one oral tablet of placebo per day for 24 months.                                                                                                                                       |                  |

### Primary: Mean rate of change from Baseline in the total area of geographic atrophy in the study eye

|                                   |                                                                                            |
|-----------------------------------|--------------------------------------------------------------------------------------------|
| End point title                   | Mean rate of change from Baseline in the total area of geographic atrophy in the study eye |
| End point description:            |                                                                                            |
| End point type                    | Primary                                                                                    |
| End point timeframe:<br>24 Months |                                                                                            |

| End point values                    | Emixustat 2.5 mg | Emixustat 5 mg  | Emixustat 10 mg | Placebo         |
|-------------------------------------|------------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group  | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 133              | 134             | 103             | 133             |
| Units: mm <sup>2</sup> per year     |                  |                 |                 |                 |
| least squares mean (standard error) | 1.69 (± 0.115)   | 1.83 (± 0.116)  | 1.84 (± 0.143)  | 1.69 (± 0.108)  |

### Statistical analyses

|                            |                                                               |
|----------------------------|---------------------------------------------------------------|
| Statistical analysis title | Least square mean difference against placebo                  |
| Comparison groups          | Emixustat 2.5 mg v Emixustat 5 mg v Emixustat 10 mg v Placebo |



|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 503                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | $\geq 0.81$ <sup>[1]</sup>     |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.15                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.2                           |
| upper limit                             | 0.5                            |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 0.18                           |

Notes:

[1] - 2.5 mg group vs. placebo group -- p = 0.99

5 mg group vs. placebo group -- p = 0.81

10 mg group vs. placebo group -- p = 0.81

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

24 months

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Emixustat 2.5 mg |
|-----------------------|------------------|

Reporting group description:

Subjects took one oral tablet of emixustat 2.5 mg per day for 24 months.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Emixustat 5 mg |
|-----------------------|----------------|

Reporting group description:

Subjects took one oral tablet of emixustat 5 mg per day for 24 months.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Emixustat 10 mg |
|-----------------------|-----------------|

Reporting group description:

Subjects took one oral tablet of emixustat 5 mg per day for 1 month, then one oral tablet of emixustat 7.5 mg per day for 1 month, and then one oral tablet of emixustat 10 mg per day for 22 months.

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

Reporting group description:

Subjects took one oral tablet of placebo per day for 24 months.

| Serious adverse events                                              | Emixustat 2.5 mg  | Emixustat 5 mg    | Emixustat 10 mg   |
|---------------------------------------------------------------------|-------------------|-------------------|-------------------|
| Total subjects affected by serious adverse events                   |                   |                   |                   |
| subjects affected / exposed                                         | 34 / 133 (25.56%) | 41 / 134 (30.60%) | 20 / 103 (19.42%) |
| number of deaths (all causes)                                       | 3                 | 2                 | 1                 |
| number of deaths resulting from adverse events                      | 3                 | 2                 | 1                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |                   |
| Adenocarcinoma of colon                                             |                   |                   |                   |
| subjects affected / exposed                                         | 1 / 133 (0.75%)   | 0 / 134 (0.00%)   | 1 / 103 (0.97%)   |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             | 0 / 0             |
| Plasma cell myeloma                                                 |                   |                   |                   |
| subjects affected / exposed                                         | 2 / 133 (1.50%)   | 0 / 134 (0.00%)   | 0 / 103 (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             |
| Prostate cancer                                                     |                   |                   |                   |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 2 / 103 (1.94%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Breast cancer                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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 lymphocytic leukaemia                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Intestinal adenocarcinoma                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Laryngeal cancer recurrent                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung adenocarcinoma                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung cancer metastatic                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Lung neoplasm malignant                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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 recurrent                       |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Salivary gland cancer                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 134 (0.75%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Breast cancer metastatic                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Small cell lung cancer limited stage            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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                              |                 |                 |                 |
| Hypotension                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 134 (0.75%) | 0 / 103 (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           |
| Orthostatic hypotension                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral artery occlusion                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 134 (0.75%) | 0 / 103 (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           |
| Accelerated hypertension                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Temporal arteritis                              |                 |                 |                 |

|                                                      |                 |                 |                 |
|------------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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 |                 |                 |                 |
| Asthenia                                             |                 |                 |                 |
| subjects affected / exposed                          | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Chest pain                                           |                 |                 |                 |
| subjects affected / exposed                          | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Death                                                |                 |                 |                 |
| subjects affected / exposed                          | 0 / 133 (0.00%) | 1 / 134 (0.75%) | 0 / 103 (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           |
| Systemic inflammatory response syndrome              |                 |                 |                 |
| subjects affected / exposed                          | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Adnexa uteri mass                                    |                 |                 |                 |
| subjects affected / exposed                          | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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      |                 |                 |                 |
| Chronic obstructive pulmonary disease                |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 3 / 133 (2.26%) | 0 / 134 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute respiratory failure                       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 133 (1.50%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Asthma                                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Dyspnoea                                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dyspnoea exertional                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 134 (0.75%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pleural effusion                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia aspiration                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Pulmonary embolism                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 134 (0.75%) | 0 / 103 (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           |
| hypoxia                                         |                 |                 |                 |

|                                                       |                 |                 |                 |
|-------------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                           | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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>                                 |                 |                 |                 |
| Cardiac murmur                                        |                 |                 |                 |
| subjects affected / exposed                           | 0 / 133 (0.00%) | 1 / 134 (0.75%) | 0 / 103 (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           |
| Transaminases increased                               |                 |                 |                 |
| subjects affected / exposed                           | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| 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>Injury, poisoning and procedural complications</b> |                 |                 |                 |
| Fall                                                  |                 |                 |                 |
| subjects affected / exposed                           | 0 / 133 (0.00%) | 6 / 134 (4.48%) | 2 / 103 (1.94%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 7           | 1 / 2           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Femur fracture                                        |                 |                 |                 |
| subjects affected / exposed                           | 1 / 133 (0.75%) | 2 / 134 (1.49%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Hip fracture                                          |                 |                 |                 |
| subjects affected / exposed                           | 0 / 133 (0.00%) | 2 / 134 (1.49%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Road traffic accident                                 |                 |                 |                 |
| subjects affected / exposed                           | 1 / 133 (0.75%) | 1 / 134 (0.75%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 1           | 0 / 0           |
| Cervical vertebral fracture                           |                 |                 |                 |
| subjects affected / exposed                           | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Concussion                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Delayed recovery from anaesthesia               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Foot fracture                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 134 (0.75%) | 0 / 103 (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           |
| Infusion related reaction                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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 / 133 (0.00%) | 1 / 134 (0.75%) | 0 / 103 (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           |
| pubis fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 134 (0.75%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rib fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Spinal compression fracture                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Subdural haematoma                              |                 |                 |                 |



|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eyelid injury                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Facial bones fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Tendon rupture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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                               |                 |                 |                 |
| Atrial fibrillation                             |                 |                 |                 |
| subjects affected / exposed                     | 3 / 133 (2.26%) | 1 / 134 (0.75%) | 2 / 103 (1.94%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 2 / 133 (1.50%) | 1 / 134 (0.75%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 2 / 103 (1.94%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Sinus node dysfunction                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 1 / 134 (0.75%) | 0 / 103 (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           |
| Angina unstable                                 |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| 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 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| 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 stenosis                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac arrest                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Cardiac failure acute                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Cardio-respiratory arrest                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Coronary artery disease                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 134 (0.75%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronary artery stenosis                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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 cardiomyopathy                        |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sinus bradycardia                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Acute myocardial infarction                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Atrioventricular block                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Ventricular tachycardia                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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                        |                 |                 |                 |
| Syncope                                         |                 |                 |                 |
| subjects affected / exposed                     | 2 / 133 (1.50%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebrovascular accident                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 2 / 103 (1.94%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Carotid artery stenosis                         |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Seizure                                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| 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 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebral infarction                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Transient ischaemic attack                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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            |                 |                 |                 |
| Anaemia                                         |                 |                 |                 |
| subjects affected / exposed                     | 3 / 133 (2.26%) | 1 / 134 (0.75%) | 0 / 103 (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           |
| Coagulopathy                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Ear and labyrinth disorders                     |                 |                 |                 |

|                                                                     |                 |                 |                 |
|---------------------------------------------------------------------|-----------------|-----------------|-----------------|
| Vertigo positional<br>subjects affected / exposed                   | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to<br>treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                       | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye disorders                                                       |                 |                 |                 |
| Optic ischaemic neuropathy<br>subjects affected / exposed           | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to<br>treatment / all                  | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                       | 0 / 0           | 0 / 0           | 0 / 0           |
| Optic neuropathy<br>subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to<br>treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                       | 0 / 0           | 0 / 0           | 0 / 0           |
| Retinal artery occlusion<br>subjects affected / exposed             | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to<br>treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                       | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                                          |                 |                 |                 |
| Small intestinal obstruction<br>subjects affected / exposed         | 0 / 133 (0.00%) | 2 / 134 (1.49%) | 0 / 103 (0.00%) |
| occurrences causally related to<br>treatment / all                  | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to<br>treatment / all                       | 0 / 0           | 0 / 0           | 0 / 0           |
| Abdominal hernia<br>subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to<br>treatment / all                  | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                       | 0 / 0           | 0 / 0           | 0 / 0           |
| Diverticulum intestinal haemorrhagic<br>subjects affected / exposed | 0 / 133 (0.00%) | 1 / 134 (0.75%) | 0 / 103 (0.00%) |
| occurrences causally related to<br>treatment / all                  | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all                       | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastric ulcer<br>subjects affected / exposed                        | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to<br>treatment / all                  | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                       | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Gastrointestinal haemorrhage                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Intestinal obstruction                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lower gastrointestinal haemorrhage              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Pancreatitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Rectal haemorrhage                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Upper gastrointestinal haemorrhage              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colitis                                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Intra-abdominal haematoma                       |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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>Hepatobiliary disorders</b>                  |                 |                 |                 |
| Bile duct obstruction                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholecystitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholelithiasis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| 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>Skin and subcutaneous tissue disorders</b>   |                 |                 |                 |
| Angioedema                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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>Renal and urinary disorders</b>              |                 |                 |                 |
| Acute kidney injury                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 134 (0.75%) | 2 / 103 (1.94%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ureterolithiasis                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| 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 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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 |                 |                 |                 |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 133 (1.50%) | 2 / 134 (1.49%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Spinal pain                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Back pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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 spinal stenosis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Spondylolisthesis                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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                     |                 |                 |                 |
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 133 (1.50%) | 2 / 134 (1.49%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sepsis                                          |                 |                 |                 |
| subjects affected / exposed                     | 2 / 133 (1.50%) | 2 / 134 (1.49%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cellulitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |



|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Appendicitis perforated                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arthritis bacterial                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atypical pneumonia                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Bronchitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Bronchopulmonary aspergillosis allergic         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Clostridium difficile colitis                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Diverticulitis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Endocarditis                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Enterocolitis infectious                        |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastroenteritis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 134 (0.75%) | 0 / 103 (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           |
| Influenza                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Parainfluenzae virus infection                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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 pseudomonal                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyelonephritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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 acute                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 134 (0.75%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Streptococcal sepsis                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Appendicitis                                    |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Escherichia sepsis                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Escherichia urinary tract infection             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Herpes zoster                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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              |                 |                 |                 |
| Hyponatraemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 134 (0.00%) | 0 / 103 (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           |
| Dehydration                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 134 (0.00%) | 0 / 103 (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           |

| Serious adverse events                            | Placebo           |  |  |
|---------------------------------------------------|-------------------|--|--|
| Total subjects affected by serious adverse events |                   |  |  |
| subjects affected / exposed                       | 30 / 133 (22.56%) |  |  |
| number of deaths (all causes)                     | 0                 |  |  |
| number of deaths resulting from adverse events    | 0                 |  |  |

|                                                                     |                 |  |  |
|---------------------------------------------------------------------|-----------------|--|--|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |  |  |
| Adenocarcinoma of colon                                             |                 |  |  |
| subjects affected / exposed                                         | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0           |  |  |
| deaths causally related to treatment / all                          | 0 / 0           |  |  |
| Plasma cell myeloma                                                 |                 |  |  |
| subjects affected / exposed                                         | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0           |  |  |
| deaths causally related to treatment / all                          | 0 / 0           |  |  |
| Prostate cancer                                                     |                 |  |  |
| subjects affected / exposed                                         | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0           |  |  |
| deaths causally related to treatment / all                          | 0 / 0           |  |  |
| Breast cancer                                                       |                 |  |  |
| subjects affected / exposed                                         | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0           |  |  |
| deaths causally related to treatment / all                          | 0 / 0           |  |  |
| Chronic lymphocytic leukaemia                                       |                 |  |  |
| subjects affected / exposed                                         | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0           |  |  |
| deaths causally related to treatment / all                          | 0 / 0           |  |  |
| Intestinal adenocarcinoma                                           |                 |  |  |
| subjects affected / exposed                                         | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0           |  |  |
| deaths causally related to treatment / all                          | 0 / 0           |  |  |
| Laryngeal cancer recurrent                                          |                 |  |  |
| subjects affected / exposed                                         | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0           |  |  |
| deaths causally related to treatment / all                          | 0 / 0           |  |  |
| Lung adenocarcinoma                                                 |                 |  |  |
| subjects affected / exposed                                         | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0           |  |  |
| deaths causally related to treatment / all                          | 0 / 0           |  |  |

|                                                                     |                 |  |  |
|---------------------------------------------------------------------|-----------------|--|--|
| Lung cancer metastatic<br>subjects affected / exposed               | 0 / 133 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all                  | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0           |  |  |
| Lung neoplasm malignant<br>subjects affected / exposed              | 1 / 133 (0.75%) |  |  |
| occurrences causally related to<br>treatment / all                  | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0           |  |  |
| Prostate cancer recurrent<br>subjects affected / exposed            | 0 / 133 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all                  | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0           |  |  |
| Salivary gland cancer<br>subjects affected / exposed                | 0 / 133 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all                  | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0           |  |  |
| Breast cancer metastatic<br>subjects affected / exposed             | 1 / 133 (0.75%) |  |  |
| occurrences causally related to<br>treatment / all                  | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0           |  |  |
| Small cell lung cancer limited stage<br>subjects affected / exposed | 1 / 133 (0.75%) |  |  |
| occurrences causally related to<br>treatment / all                  | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0           |  |  |
| Vascular disorders                                                  |                 |  |  |
| Hypotension<br>subjects affected / exposed                          | 1 / 133 (0.75%) |  |  |
| occurrences causally related to<br>treatment / all                  | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0           |  |  |
| Orthostatic hypotension<br>subjects affected / exposed              | 0 / 133 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all                  | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0           |  |  |
| Peripheral artery occlusion                                         |                 |  |  |

|                                                      |                 |  |  |
|------------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                          | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Accelerated hypertension                             |                 |  |  |
| subjects affected / exposed                          | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Temporal arteritis                                   |                 |  |  |
| subjects affected / exposed                          | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Asthenia                                             |                 |  |  |
| subjects affected / exposed                          | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Chest pain                                           |                 |  |  |
| subjects affected / exposed                          | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Death                                                |                 |  |  |
| subjects affected / exposed                          | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Systemic inflammatory response syndrome              |                 |  |  |
| subjects affected / exposed                          | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Reproductive system and breast disorders             |                 |  |  |
| Cystocele                                            |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Adnexa uteri mass                               |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Chronic obstructive pulmonary disease           |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Acute respiratory failure                       |                 |  |  |
| subjects affected / exposed                     | 2 / 133 (1.50%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Asthma                                          |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dyspnoea                                        |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dyspnoea exertional                             |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pleural effusion                                |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia aspiration                            |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary embolism                              |                 |  |  |
| subjects affected / exposed                     | 2 / 133 (1.50%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| hypoxia                                         |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Investigations                                  |                 |  |  |
| Cardiac murmur                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Transaminases increased                         |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| Fall                                            |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Femur fracture                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hip fracture                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |



|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| Road traffic accident                           |                 |  |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cervical vertebral fracture                     |                 |  |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Concussion                                      |                 |  |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Delayed recovery from anaesthesia               |                 |  |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Foot fracture                                   |                 |  |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Infusion related reaction                       |                 |  |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Lumbar vertebral fracture                       |                 |  |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| pubis fracture                                  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Rib fracture                                    |                 |  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Spinal compression fracture                     |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Subdural haematoma                              |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Eyelid injury                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Facial bones fracture                           |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tendon rupture                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Atrial fibrillation                             |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Myocardial infarction                           |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac failure congestive                      |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Sinus node dysfunction                          |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Angina unstable                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Aortic valve incompetence                       |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Aortic valve stenosis                           |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac arrest                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac failure acute                           |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardio-respiratory arrest                       |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Coronary artery disease                         |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Coronary artery stenosis                        |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ischaemic cardiomyopathy                        |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Sinus bradycardia                               |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Acute myocardial infarction                     |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Angina pectoris                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atrioventricular block                          |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ventricular tachycardia                         |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nervous system disorders                        |                 |  |  |
| Syncope                                         |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 4 / 133 (3.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cerebrovascular accident                        |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Carotid artery stenosis                         |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dizziness                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Seizure                                         |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Subarachnoid haemorrhage                        |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cerebral infarction                             |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Transient ischaemic attack                      |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood and lymphatic system disorders            |                 |  |  |
| Anaemia                                         |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Coagulopathy                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ear and labyrinth disorders                     |                 |  |  |
| Vertigo positional                              |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Eye disorders                                   |                 |  |  |
| Optic ischaemic neuropathy                      |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Optic neuropathy                                |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Retinal artery occlusion                        |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Small intestinal obstruction                    |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Abdominal hernia                                |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|                                                                     |                 |  |  |  |
|---------------------------------------------------------------------|-----------------|--|--|--|
| Diverticulum intestinal haemorrhagic<br>subjects affected / exposed | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to<br>treatment / all                  | 0 / 0           |  |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0           |  |  |  |
| Gastric ulcer<br>subjects affected / exposed                        | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to<br>treatment / all                  | 0 / 0           |  |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0           |  |  |  |
| Gastrointestinal haemorrhage<br>subjects affected / exposed         | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to<br>treatment / all                  | 0 / 0           |  |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0           |  |  |  |
| Intestinal obstruction<br>subjects affected / exposed               | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to<br>treatment / all                  | 0 / 0           |  |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0           |  |  |  |
| Lower gastrointestinal haemorrhage<br>subjects affected / exposed   | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to<br>treatment / all                  | 0 / 0           |  |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0           |  |  |  |
| Pancreatitis<br>subjects affected / exposed                         | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to<br>treatment / all                  | 0 / 0           |  |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0           |  |  |  |
| Rectal haemorrhage<br>subjects affected / exposed                   | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to<br>treatment / all                  | 0 / 0           |  |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0           |  |  |  |
| Upper gastrointestinal haemorrhage<br>subjects affected / exposed   | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to<br>treatment / all                  | 0 / 0           |  |  |  |
| deaths causally related to<br>treatment / all                       | 0 / 0           |  |  |  |
| Colitis                                                             |                 |  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 2 / 133 (1.50%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Inguinal hernia                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intra-abdominal haematoma                       |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| Bile duct obstruction                           |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cholecystitis                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cholelithiasis                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skin and subcutaneous tissue disorders          |                 |  |  |
| Angioedema                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Acute kidney injury                             |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |



|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| Ureterolithiasis                                |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal failure                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Osteoarthritis                                  |                 |  |  |
| subjects affected / exposed                     | 4 / 133 (3.01%) |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Spinal pain                                     |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Back pain                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lumbar spinal stenosis                          |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Spondylolisthesis                               |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Pneumonia                                       |                 |  |  |
| subjects affected / exposed                     | 3 / 133 (2.26%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| Sepsis                                          |                 |  |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cellulitis                                      |                 |  |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Appendicitis perforated                         |                 |  |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Arthritis bacterial                             |                 |  |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Atypical pneumonia                              |                 |  |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Bronchitis                                      |                 |  |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Bronchopulmonary aspergillosis allergic         |                 |  |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Clostridium difficile colitis                   |                 |  |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Diverticulitis                                  |                 |  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Endocarditis                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Enterocolitis infectious                        |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastroenteritis                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Influenza                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Parainfluenzae virus infection                  |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia pseudomonal                           |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pyelonephritis                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pyelonephritis acute                            |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Streptococcal sepsis                            |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Appendicitis                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Escherichia sepsis                              |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Escherichia urinary tract infection             |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Herpes zoster                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urinary tract infection                         |                 |  |  |
| subjects affected / exposed                     | 2 / 133 (1.50%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Hyponatraemia                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dehydration                                     |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 133 (0.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

| <b>Non-serious adverse events</b>                     | Emixustat 2.5 mg   | Emixustat 5 mg     | Emixustat 10 mg    |
|-------------------------------------------------------|--------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events |                    |                    |                    |
| subjects affected / exposed                           | 127 / 133 (95.49%) | 131 / 134 (97.76%) | 101 / 103 (98.06%) |
| Investigations                                        |                    |                    |                    |
| Visual acuity tests abnormal                          |                    |                    |                    |
| subjects affected / exposed                           | 9 / 133 (6.77%)    | 19 / 134 (14.18%)  | 14 / 103 (13.59%)  |
| occurrences (all)                                     | 9                  | 25                 | 16                 |
| Injury, poisoning and procedural complications        |                    |                    |                    |
| Fall                                                  |                    |                    |                    |
| subjects affected / exposed                           | 7 / 133 (5.26%)    | 14 / 134 (10.45%)  | 8 / 103 (7.77%)    |
| occurrences (all)                                     | 7                  | 16                 | 13                 |
| Vascular disorders                                    |                    |                    |                    |
| Hypertension                                          |                    |                    |                    |
| subjects affected / exposed                           | 12 / 133 (9.02%)   | 11 / 134 (8.21%)   | 5 / 103 (4.85%)    |
| occurrences (all)                                     | 13                 | 14                 | 6                  |
| Cardiac disorders                                     |                    |                    |                    |
| Atrial fibrillation                                   |                    |                    |                    |
| subjects affected / exposed                           | 6 / 133 (4.51%)    | 3 / 134 (2.24%)    | 0 / 103 (0.00%)    |
| occurrences (all)                                     | 6                  | 4                  | 0                  |
| Nervous system disorders                              |                    |                    |                    |
| Visual field defect                                   |                    |                    |                    |
| subjects affected / exposed                           | 7 / 133 (5.26%)    | 10 / 134 (7.46%)   | 12 / 103 (11.65%)  |
| occurrences (all)                                     | 8                  | 13                 | 13                 |
| Headache                                              |                    |                    |                    |
| subjects affected / exposed                           | 5 / 133 (3.76%)    | 11 / 134 (8.21%)   | 6 / 103 (5.83%)    |
| occurrences (all)                                     | 6                  | 13                 | 8                  |
| Dizziness                                             |                    |                    |                    |
| subjects affected / exposed                           | 5 / 133 (3.76%)    | 7 / 134 (5.22%)    | 2 / 103 (1.94%)    |
| occurrences (all)                                     | 5                  | 9                  | 2                  |
| Blood and lymphatic system disorders                  |                    |                    |                    |

|                                                                                                                                  |                         |                          |                         |
|----------------------------------------------------------------------------------------------------------------------------------|-------------------------|--------------------------|-------------------------|
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                                                                      | 7 / 133 (5.26%)<br>7    | 4 / 134 (2.99%)<br>4     | 5 / 103 (4.85%)<br>6    |
| General disorders and administration<br>site conditions<br>Oedema peripheral<br>subjects affected / exposed<br>occurrences (all) | 6 / 133 (4.51%)<br>7    | 2 / 134 (1.49%)<br>2     | 1 / 103 (0.97%)<br>1    |
| Eye disorders<br>Delayed dark adaptation<br>subjects affected / exposed<br>occurrences (all)                                     | 48 / 133 (36.09%)<br>56 | 88 / 134 (65.67%)<br>105 | 69 / 103 (66.99%)<br>87 |
| Chromatopsia<br>subjects affected / exposed<br>occurrences (all)                                                                 | 13 / 133 (9.77%)<br>13  | 30 / 134 (22.39%)<br>35  | 22 / 103 (21.36%)<br>23 |
| Visual impairment<br>subjects affected / exposed<br>occurrences (all)                                                            | 12 / 133 (9.02%)<br>14  | 25 / 134 (18.66%)<br>42  | 20 / 103 (19.42%)<br>25 |
| Erythropsia<br>subjects affected / exposed<br>occurrences (all)                                                                  | 12 / 133 (9.02%)<br>15  | 26 / 134 (19.40%)<br>33  | 16 / 103 (15.53%)<br>19 |
| Visual acuity reduced<br>subjects affected / exposed<br>occurrences (all)                                                        | 18 / 133 (13.53%)<br>22 | 18 / 134 (13.43%)<br>22  | 13 / 103 (12.62%)<br>15 |
| Vision blurred<br>subjects affected / exposed<br>occurrences (all)                                                               | 10 / 133 (7.52%)<br>10  | 17 / 134 (12.69%)<br>18  | 16 / 103 (15.53%)<br>18 |
| Choroidal neovascularisation<br>subjects affected / exposed<br>occurrences (all)                                                 | 17 / 133 (12.78%)<br>19 | 10 / 134 (7.46%)<br>11   | 8 / 103 (7.77%)<br>10   |
| Retinal haemorrhage<br>subjects affected / exposed<br>occurrences (all)                                                          | 8 / 133 (6.02%)<br>10   | 15 / 134 (11.19%)<br>16  | 8 / 103 (7.77%)<br>10   |
| Posterior capsule opacification<br>subjects affected / exposed<br>occurrences (all)                                              | 5 / 133 (3.76%)<br>6    | 13 / 134 (9.70%)<br>16   | 9 / 103 (8.74%)<br>11   |
| Vitreous detachment                                                                                                              |                         |                          |                         |

|                                                                                             |                        |                        |                        |
|---------------------------------------------------------------------------------------------|------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)                                            | 10 / 133 (7.52%)<br>12 | 10 / 134 (7.46%)<br>11 | 5 / 103 (4.85%)<br>5   |
| Cataract nuclear<br>subjects affected / exposed<br>occurrences (all)                        | 9 / 133 (6.77%)<br>13  | 11 / 134 (8.21%)<br>16 | 4 / 103 (3.88%)<br>4   |
| Xanthopsia<br>subjects affected / exposed<br>occurrences (all)                              | 2 / 133 (1.50%)<br>3   | 10 / 134 (7.46%)<br>10 | 9 / 103 (8.74%)<br>9   |
| Night blindness<br>subjects affected / exposed<br>occurrences (all)                         | 4 / 133 (3.01%)<br>4   | 3 / 134 (2.24%)<br>3   | 10 / 103 (9.71%)<br>14 |
| Cataract cortical<br>subjects affected / exposed<br>occurrences (all)                       | 6 / 133 (4.51%)<br>11  | 6 / 134 (4.48%)<br>9   | 4 / 103 (3.88%)<br>7   |
| Blepharitis<br>subjects affected / exposed<br>occurrences (all)                             | 2 / 133 (1.50%)<br>2   | 7 / 134 (5.22%)<br>8   | 3 / 103 (2.91%)<br>3   |
| Cyanopsia<br>subjects affected / exposed<br>occurrences (all)                               | 2 / 133 (1.50%)<br>2   | 9 / 134 (6.72%)<br>9   | 1 / 103 (0.97%)<br>1   |
| Dry age-related macular<br>degeneration<br>subjects affected / exposed<br>occurrences (all) | 3 / 133 (2.26%)<br>3   | 2 / 134 (1.49%)<br>2   | 6 / 103 (5.83%)<br>6   |
| Punctate keratitis<br>subjects affected / exposed<br>occurrences (all)                      | 3 / 133 (2.26%)<br>3   | 3 / 134 (2.24%)<br>3   | 3 / 103 (2.91%)<br>3   |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)    | 4 / 133 (3.01%)<br>5   | 6 / 134 (4.48%)<br>6   | 5 / 103 (4.85%)<br>6   |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                               | 4 / 133 (3.01%)<br>4   | 6 / 134 (4.48%)<br>7   | 2 / 103 (1.94%)<br>2   |
| Respiratory, thoracic and mediastinal<br>disorders                                          |                        |                        |                        |

|                                                                             |                         |                        |                      |
|-----------------------------------------------------------------------------|-------------------------|------------------------|----------------------|
| Cough<br>subjects affected / exposed<br>occurrences (all)                   | 8 / 133 (6.02%)<br>10   | 7 / 134 (5.22%)<br>7   | 3 / 103 (2.91%)<br>3 |
| Musculoskeletal and connective tissue disorders                             |                         |                        |                      |
| Back pain<br>subjects affected / exposed<br>occurrences (all)               | 7 / 133 (5.26%)<br>7    | 5 / 134 (3.73%)<br>6   | 6 / 103 (5.83%)<br>6 |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)              | 2 / 133 (1.50%)<br>3    | 6 / 134 (4.48%)<br>8   | 2 / 103 (1.94%)<br>2 |
| Infections and infestations                                                 |                         |                        |                      |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)         | 15 / 133 (11.28%)<br>21 | 12 / 134 (8.96%)<br>12 | 7 / 103 (6.80%)<br>8 |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)              | 11 / 133 (8.27%)<br>12  | 5 / 134 (3.73%)<br>5   | 8 / 103 (7.77%)<br>8 |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 7 / 133 (5.26%)<br>12   | 4 / 134 (2.99%)<br>6   | 6 / 103 (5.83%)<br>7 |
| Herpes zoster<br>subjects affected / exposed<br>occurrences (all)           | 2 / 133 (1.50%)<br>2    | 1 / 134 (0.75%)<br>1   | 2 / 103 (1.94%)<br>2 |

|                                                                                      |                         |  |  |
|--------------------------------------------------------------------------------------|-------------------------|--|--|
| <b>Non-serious adverse events</b>                                                    | Placebo                 |  |  |
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 127 / 133 (95.49%)      |  |  |
| Investigations                                                                       |                         |  |  |
| Visual acuity tests abnormal<br>subjects affected / exposed<br>occurrences (all)     | 9 / 133 (6.77%)<br>9    |  |  |
| Injury, poisoning and procedural complications                                       |                         |  |  |
| Fall<br>subjects affected / exposed<br>occurrences (all)                             | 20 / 133 (15.04%)<br>26 |  |  |
| Vascular disorders                                                                   |                         |  |  |



|                                                                                                                                                                                                                                                                      |                                                                                   |  |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|--|--|
| Hypertension<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                     | 17 / 133 (12.78%)<br>20                                                           |  |  |
| Cardiac disorders<br>Atrial fibrillation<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                         | 7 / 133 (5.26%)<br>8                                                              |  |  |
| Nervous system disorders<br>Visual field defect<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Dizziness<br>subjects affected / exposed<br>occurrences (all)                         | 2 / 133 (1.50%)<br>2<br><br>13 / 133 (9.77%)<br>18<br><br>9 / 133 (6.77%)<br>11   |  |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                  | 1 / 133 (0.75%)<br>1                                                              |  |  |
| General disorders and administration<br>site conditions<br>Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                     | 14 / 133 (10.53%)<br>17                                                           |  |  |
| Eye disorders<br>Delayed dark adaptation<br>subjects affected / exposed<br>occurrences (all)<br><br>Chromatopsia<br>subjects affected / exposed<br>occurrences (all)<br><br>Visual impairment<br>subjects affected / exposed<br>occurrences (all)<br><br>Erythropsia | 13 / 133 (9.77%)<br>15<br><br>4 / 133 (3.01%)<br>4<br><br>19 / 133 (14.29%)<br>32 |  |  |

|                                 |                   |  |  |
|---------------------------------|-------------------|--|--|
| subjects affected / exposed     | 6 / 133 (4.51%)   |  |  |
| occurrences (all)               | 6                 |  |  |
| Visual acuity reduced           |                   |  |  |
| subjects affected / exposed     | 18 / 133 (13.53%) |  |  |
| occurrences (all)               | 24                |  |  |
| Vision blurred                  |                   |  |  |
| subjects affected / exposed     | 10 / 133 (7.52%)  |  |  |
| occurrences (all)               | 11                |  |  |
| Choroidal neovascularisation    |                   |  |  |
| subjects affected / exposed     | 17 / 133 (12.78%) |  |  |
| occurrences (all)               | 30                |  |  |
| Retinal haemorrhage             |                   |  |  |
| subjects affected / exposed     | 11 / 133 (8.27%)  |  |  |
| occurrences (all)               | 15                |  |  |
| Posterior capsule opacification |                   |  |  |
| subjects affected / exposed     | 7 / 133 (5.26%)   |  |  |
| occurrences (all)               | 10                |  |  |
| Vitreous detachment             |                   |  |  |
| subjects affected / exposed     | 11 / 133 (8.27%)  |  |  |
| occurrences (all)               | 14                |  |  |
| Cataract nuclear                |                   |  |  |
| subjects affected / exposed     | 13 / 133 (9.77%)  |  |  |
| occurrences (all)               | 22                |  |  |
| Xanthopsia                      |                   |  |  |
| subjects affected / exposed     | 1 / 133 (0.75%)   |  |  |
| occurrences (all)               | 1                 |  |  |
| Night blindness                 |                   |  |  |
| subjects affected / exposed     | 1 / 133 (0.75%)   |  |  |
| occurrences (all)               | 1                 |  |  |
| Cataract cortical               |                   |  |  |
| subjects affected / exposed     | 7 / 133 (5.26%)   |  |  |
| occurrences (all)               | 9                 |  |  |
| Blepharitis                     |                   |  |  |
| subjects affected / exposed     | 4 / 133 (3.01%)   |  |  |
| occurrences (all)               | 5                 |  |  |
| Cyanopsia                       |                   |  |  |

|                                                 |                   |  |  |
|-------------------------------------------------|-------------------|--|--|
| subjects affected / exposed                     | 0 / 133 (0.00%)   |  |  |
| occurrences (all)                               | 0                 |  |  |
| Dry age-related macular degeneration            |                   |  |  |
| subjects affected / exposed                     | 6 / 133 (4.51%)   |  |  |
| occurrences (all)                               | 6                 |  |  |
| Punctate keratitis                              |                   |  |  |
| subjects affected / exposed                     | 7 / 133 (5.26%)   |  |  |
| occurrences (all)                               | 9                 |  |  |
| Gastrointestinal disorders                      |                   |  |  |
| Nausea                                          |                   |  |  |
| subjects affected / exposed                     | 11 / 133 (8.27%)  |  |  |
| occurrences (all)                               | 12                |  |  |
| Diarrhoea                                       |                   |  |  |
| subjects affected / exposed                     | 15 / 133 (11.28%) |  |  |
| occurrences (all)                               | 25                |  |  |
| Respiratory, thoracic and mediastinal disorders |                   |  |  |
| Cough                                           |                   |  |  |
| subjects affected / exposed                     | 12 / 133 (9.02%)  |  |  |
| occurrences (all)                               | 13                |  |  |
| Musculoskeletal and connective tissue disorders |                   |  |  |
| Back pain                                       |                   |  |  |
| subjects affected / exposed                     | 5 / 133 (3.76%)   |  |  |
| occurrences (all)                               | 8                 |  |  |
| Arthralgia                                      |                   |  |  |
| subjects affected / exposed                     | 7 / 133 (5.26%)   |  |  |
| occurrences (all)                               | 8                 |  |  |
| Infections and infestations                     |                   |  |  |
| Nasopharyngitis                                 |                   |  |  |
| subjects affected / exposed                     | 27 / 133 (20.30%) |  |  |
| occurrences (all)                               | 38                |  |  |
| Bronchitis                                      |                   |  |  |
| subjects affected / exposed                     | 8 / 133 (6.02%)   |  |  |
| occurrences (all)                               | 8                 |  |  |
| Urinary tract infection                         |                   |  |  |

|                             |                   |  |  |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 17 / 133 (12.78%) |  |  |
| occurrences (all)           | 18                |  |  |
| Herpes zoster               |                   |  |  |
| subjects affected / exposed | 7 / 133 (5.26%)   |  |  |
| occurrences (all)           | 8                 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                 |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 25 March 2013    | Added exclusion of subjects with known allergy to active pharmaceutical ingredient or excipients                                                                                                                          |
| 03 June 2013     | Added further details to several exclusion criteria. Clarified that subjects who develop choroidal neovascularization or who are unmasked must be withdrawn from the study. Clarified prohibited concomitant medications. |
| 07 November 2013 | Added intraocular pressure and low luminance visual acuity to more visits. Instituted unscheduled visits to be performed in instances of decreased visual acuity.                                                         |
| 17 December 2013 | Increased sample size.                                                                                                                                                                                                    |
| 01 October 2014  | Omitted interim analyses.                                                                                                                                                                                                 |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29716784>