



## Clinical trial results:

**Randomised phase III multicentric study comparing efficacy of doxorubicin with trabectedin followed by trabectedin in non-progressive patients versus doxorubicine alone as first-line therapy in patients with metastatic or unresectable leiomyosarcoma (uterine or soft tissue)**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2016-002186-56 |
| Trial protocol           | FR             |
| Global end of trial date | 26 April 2022  |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 15 December 2022 |
| First version publication date | 15 December 2022 |

### Trial information

#### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | 2016/2410 |
|-----------------------|-----------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Gustave Roussy  |
| Sponsor organisation address | 114 Rue Edouard Vaillant, Villejuif, France, 94805  |
| Public contact               | Benjamin BESSE<br>Direction de la Recherche Clinique<br>Bureau Projets et Promotion<br>, GUSTAVE ROUSSY, FR +33142116717,<br>bpp.regulatory@gustaveroussy.fr  |
| Scientific contact           | Benjamin BESSE<br>Direction de la Recherche Clinique-<br>Bureau Projets et Promotion<br>, GUSTAVE ROUSSY, FR +33142116717,<br>bpp.regulatory@gustaveroussy.fr |

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                       | 26 April 2022 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 26 April 2022 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 26 April 2022 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

Determine and compare the progression-free survival (PFS) of patients treated in first line with doxorubicin alone or with the association of doxorubicin and trabectedin followed by trabectedin for non-progressive patients

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial subjects.

Background therapy: -

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 19 September 2016 |
| Long term follow-up planned                               | No                |
| Independent data monitoring committee (IDMC) involvement? | No                |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | France: 150 |
| Worldwide total number of subjects   | 150         |
| EEA total number of subjects         | 150         |

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)                      | 89 |

|                     |    |
|---------------------|----|
| From 65 to 84 years | 60 |
| 85 years and over   | 1  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 150 subjects were enrolled in this study, and 1 of them did not receive any therapy.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | overall study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Not blinded                    |

### Arms

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

Arm description:

Trabectedin was to be administered at the dose of 1.1 mg/m<sup>2</sup> via central venous access over 3 hours on day 1 of each 3-week cycle in two treatment periods. Commercially available doxorubicin was to be administered at the dose of 60 mg/m<sup>2</sup> via central venous access over 10 to 15 minutes on day 1 of each 3-week cycle, for a maximum of six cycles or until premature discontinuation of treatment. An injection of pegfilgrastim 6 mg (pegylated G-CSF) per subcutaneous route was given on day 2. During the initial treatment period, trabectedin was to be administered in combination with doxorubicin for a maximum of six cycles or until premature discontinuation of treatment. During the maintenance treatment period, patients with a response after the six cycles of initial treatment were to be given trabectedin at the same dose and schedule as during the initial treatment for a maximum of 17 cycles (12 months) or until premature discontinuation of treatment.

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | trabectedine          |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Trabectedin was to be administered (after 20 mg dexamethasone premedication given 30 min before) at the dose of 1.1 mg/m<sup>2</sup> via central venous access over 3 hours on day 1 of each 3-week cycle in two treatment periods. During the initial treatment period, trabectedin was to be administered in combination with doxorubicin for a maximum of six cycles or until premature discontinuation of treatment. During the maintenance treatment period, patients with a response after the six cycles of initial treatment were to be given trabectedin at the same dose and schedule as during the initial treatment (even if dose reduction was performed during the initial period) for a maximum of 17 cycles (12 months) or until premature discontinuation of treatment.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | active comparator |
|------------------|-------------------|

Arm description:

Commercially available doxorubicin was to be administered at the dose of 75 mg/m<sup>2</sup> via central venous access over 10 to 15 minutes on day 1 of each 3-week cycle, for a maximum of six cycles or until premature discontinuation of treatment. Lenograstim (G-CSF) was administered per subcutaneous route at the dose of 150 µg/m<sup>2</sup> once a day from Day 3 to Day 9

|  |                       |
|--|-----------------------|
| Arm type                               | Active comparator     |
| Investigational medicinal product name | doxorubicine          |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

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**Dosage and administration details:**

Commercially available doxorubicin was to be administered at the dose of 75 mg/m<sup>2</sup> via central venous access over 10 to 15 minutes on day 1 of each 3-week cycle, for a maximum of six cycles or until premature discontinuation of treatment.

| <b>Number of subjects in period 1</b> | experimental | active comparator |
|---------------------------------------|--------------|-------------------|
| Started                               | 74           | 76                |
| Completed                             | 60           | 54                |
| Not completed                         | 14           | 22                |
| Adverse event, serious fatal          | 7            | 3                 |
| Consent withdrawn by subject          | 2            | -                 |
| randomized but not treated            | -            | 1                 |
| progression                           | 5            | 17                |
| other                                 | -            | 1                 |

## Baseline characteristics

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | experimental |
|-----------------------|--------------|

Reporting group description:

Trabectedin was to be administered at the dose of 1.1 mg/m<sup>2</sup> via central venous access over 3 hours on day 1 of each 3-week cycle in two treatment periods. Commercially available doxorubicin was to be administered at the dose of 60 mg/m<sup>2</sup> via central venous access over 10 to 15 minutes on day 1 of each 3-week cycle, for a maximum of six cycles or until premature discontinuation of treatment. An injection of pegfilgrastim 6 mg (pegylated G-CSF) per subcutaneous route was given on day 2. During the initial treatment period, trabectedin was to be administered in combination with doxorubicin for a maximum of six cycles or until premature discontinuation of treatment. During the maintenance treatment period, patients with a response after the six cycles of initial treatment were to be given trabectedin at the same dose and schedule as during the initial treatment for a maximum of 17 cycles (12 months) or until premature discontinuation of treatment.

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | active comparator |
|-----------------------|-------------------|

Reporting group description:

Commercially available doxorubicin was to be administered at the dose of 75 mg/m<sup>2</sup> via central venous access over 10 to 15 minutes on day 1 of each 3-week cycle, for a maximum of six cycles or until premature discontinuation of treatment. Lenograstim (G-CSF) was administered per subcutaneous route at the dose of 150 µg/m<sup>2</sup> once a day from Day 3 to Day 9

| Reporting group values                                | experimental | active comparator | Total |
|---|--------------|-------------------|-------|
| Number of subjects                                    | 74           | 76                | 150   |
| Age categorical<br>Units: Subjects                    |              |                   |       |
| In utero  |              |                   | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) |              |                   | 0     |
| Newborns (0-27 days)                                  |              |                   | 0     |
| Infants and toddlers (28 days-23<br>months)           |              |                   | 0     |
| Children (2-11 years)                                 |              |                   | 0     |
| Adolescents (12-17 years)                             |              |                   | 0     |
| Adults (18-64 years)                                  |              |                   | 0     |
| From 65-84 years                                      |              |                   | 0     |
| 85 years and over                                     |              |                   | 0     |
| Age continuous<br>Units: years                        |              |                   |       |
| median  | 59           | 64                |       |
| inter-quartile range (Q1-Q3)                          | 52 to 68     | 53 to 69          | -     |
| Gender categorical<br>Units: Subjects                 |              |                   |       |
| Female  | 53           | 59                | 112   |
| Male  | 21           | 17                | 38    |

### Subject analysis sets

|                            |              |
|----------------------------|--------------|
| Subject analysis set title | Efficacy set |
|----------------------------|--------------|

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

Subject analysis set description:

All randomized patients

| Reporting group values  | Efficacy set   |  |  |
|---|----------------|--|--|
| Number of subjects  | 150            |  |  |
| 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<br>median<br>inter-quartile range (Q1-Q3)  | 61<br>52 to 68 |  |  |
| Gender categorical<br>Units: Subjects   |                |  |  |
| Female  | 112            |  |  |
| Male  | 38             |  |  |

## End points

### End points reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | experimental |
|-----------------------|--------------|

Reporting group description:

Trabectedin was to be administered at the dose of 1.1 mg/m<sup>2</sup> via central venous access over 3 hours on day 1 of each 3-week cycle in two treatment periods. Commercially available doxorubicin was to be administered at the dose of 60 mg/m<sup>2</sup> via central venous access over 10 to 15 minutes on day 1 of each 3-week cycle, for a maximum of six cycles or until premature discontinuation of treatment. An injection of pegfilgrastim 6 mg (pegylated G-CSF) per subcutaneous route was given on day 2. During the initial treatment period, trabectedin was to be administered in combination with doxorubicin for a maximum of six cycles or until premature discontinuation of treatment. During the maintenance treatment period, patients with a response after the six cycles of initial treatment were to be given trabectedin at the same dose and schedule as during the initial treatment for a maximum of 17 cycles (12 months) or until premature discontinuation of treatment.

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | active comparator |
|-----------------------|-------------------|

Reporting group description:

Commercially available doxorubicin was to be administered at the dose of 75 mg/m<sup>2</sup> via central venous access over 10 to 15 minutes on day 1 of each 3-week cycle, for a maximum of six cycles or until premature discontinuation of treatment. Lenograstim (G-CSF) was administered per subcutaneous route at the dose of 150 µg/m<sup>2</sup> once a day from Day 3 to Day 9

|                            |              |
|----------------------------|--------------|
| Subject analysis set title | Efficacy set |
|----------------------------|--------------|

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

Subject analysis set description:

All randomized patients

### Primary: Progression -free survival (PFS)

|                 |                                  |
|-----------------|----------------------------------|
| End point title | Progression -free survival (PFS) |
|-----------------|----------------------------------|

End point description:

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

End point timeframe:

24 months

| End point values            | experimental    | active comparator | Efficacy set         |  |
|-----------------------------|-----------------|-------------------|----------------------|--|
| Subject group type          | Reporting group | Reporting group   | Subject analysis set |  |
| Number of subjects analysed | 74              | 76                | 150                  |  |
| Units: percentage           | 30              | 5                 | 150                  |  |

### Statistical analyses

|                            |                  |
|----------------------------|------------------|
| Statistical analysis title | Primary analysis |
|----------------------------|------------------|

|                   |   |
|-------------------|---|
| Comparison groups | active comparator v experimental v Efficacy set |
|-------------------|---|



|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 300                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | < 0.0001 <sup>[1]</sup> |
| Method                                  | Regression, Cox         |
| Parameter estimate                      | Hazard ratio (HR)       |
| Point estimate                          | 0.41                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.29                    |
| upper limit                             | 0.58                    |

Notes:

[1] - LMS-04 met its primary endpoint, demonstrating a statistically significant improvement in progression-free-survival with the doxorubicin + trabectedin combination compared with standard-of-care in first-line treatment of metastatic leiomyosarcomas.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

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

### Dictionary used

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

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

### Reporting groups

|                       |       |
|-----------------------|-------|
| Reporting group title | ARM A |
|-----------------------|-------|

Reporting group description: -

|                       |       |
|-----------------------|-------|
| Reporting group title | ARM B |
|-----------------------|-------|

Reporting group description: -

| Serious adverse events  | ARM A   | ARM B            |  |
|---|---|------------------|--|
| Total subjects affected by serious adverse events                   |   |                  |  |
| subjects affected / exposed   | 20 / 75 (26.67%)                                | 37 / 74 (50.00%) |  |
| number of deaths (all causes)                                       | 1   | 0                |  |
| number of deaths resulting from adverse events                      | 1   | 0                |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |                  |  |
| Acute myeloid leukaemia   | Additional description: Acute myeloid leukaemia |                  |  |
| subjects affected / exposed   | 0 / 75 (0.00%)                                  | 1 / 74 (1.35%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0   | 0 / 1            |  |
| deaths causally related to treatment / all                          | 0 / 0   | 0 / 0            |  |
| Vascular disorders  |   |                  |  |
| Hypertension  | Additional description: Hypertension            |                  |  |
| subjects affected / exposed   | 0 / 75 (0.00%)                                  | 1 / 74 (1.35%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0   | 0 / 1            |  |
| deaths causally related to treatment / all                          | 0 / 0   | 0 / 0            |  |
| Shock haemorrhagic  | Additional description: Shock haemorrhagic      |                  |  |
| subjects affected / exposed   | 0 / 75 (0.00%)                                  | 1 / 74 (1.35%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0   | 0 / 1            |  |
| deaths causally related to treatment / all                          | 0 / 0   | 0 / 0            |  |
| General disorders and administration site conditions                |   |                  |  |

|  |   |                |                |
|--|---|----------------|----------------|
| Extravasation                            | Additional description: Extravasation                         |                |                |
|  | subjects affected / exposed                                   | 1 / 75 (1.33%) | 0 / 74 (0.00%) |
|  | occurrences causally related to treatment / all               | 1 / 1          | 0 / 0          |
|  | deaths causally related to treatment / all                    | 0 / 0          | 0 / 0          |
| Fatigue                                  | Additional description: Fatigue                               |                |                |
|  | subjects affected / exposed                                   | 0 / 75 (0.00%) | 2 / 74 (2.70%) |
|  | occurrences causally related to treatment / all               | 0 / 0          | 2 / 2          |
|  | deaths causally related to treatment / all                    | 0 / 0          | 0 / 0          |
| General physical health deterioration    | Additional description: General physical health deterioration |                |                |
|  | subjects affected / exposed                                   | 0 / 75 (0.00%) | 3 / 74 (4.05%) |
|  | occurrences causally related to treatment / all               | 0 / 0          | 2 / 4          |
|  | deaths causally related to treatment / all                    | 0 / 0          | 0 / 0          |
| Hyperthermia                             | Additional description: Hyperthermia                          |                |                |
|  | subjects affected / exposed                                   | 0 / 75 (0.00%) | 1 / 74 (1.35%) |
|  | occurrences causally related to treatment / all               | 0 / 0          | 1 / 1          |
|  | deaths causally related to treatment / all                    | 0 / 0          | 0 / 0          |
| Oedema                                   | Additional description: Oedema                                |                |                |
|  | subjects affected / exposed                                   | 1 / 75 (1.33%) | 0 / 74 (0.00%) |
|  | occurrences causally related to treatment / all               | 0 / 1          | 0 / 0          |
|  | deaths causally related to treatment / all                    | 0 / 0          | 0 / 0          |
| Oedema peripheral                        | Additional description: Oedema peripheral                     |                |                |
|  | subjects affected / exposed                                   | 0 / 75 (0.00%) | 1 / 74 (1.35%) |
|  | occurrences causally related to treatment / all               | 0 / 0          | 0 / 1          |
|  | deaths causally related to treatment / all                    | 0 / 0          | 0 / 0          |
| Pyrexia                                  | Additional description: Pyrexia                               |                |                |
|  | subjects affected / exposed                                   | 1 / 75 (1.33%) | 1 / 74 (1.35%) |
|  | occurrences causally related to treatment / all               | 1 / 2          | 0 / 1          |
|  | deaths causally related to treatment / all                    | 0 / 0          | 0 / 0          |
| Reproductive system and breast disorders |   |                |                |
| Intermenstrual bleeding                  | Additional description: Intermenstrual bleeding               |                |                |
|  | subjects affected / exposed                                   | 1 / 75 (1.33%) | 0 / 74 (0.00%) |
|  | occurrences causally related to treatment / all               | 0 / 1          | 0 / 0          |
|  | deaths causally related to treatment / all                    | 0 / 0          | 0 / 0          |

|   |   |                |  |
|---|---|----------------|--|
| Respiratory, thoracic and mediastinal disorders |   |                |  |
| Acute pulmonary oedema                          | Additional description: Acute pulmonary oedema              |                |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)  | 1 / 74 (1.35%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Dyspnoea  | Additional description: Dyspnoea                            |                |  |
| subjects affected / exposed                     | 1 / 75 (1.33%)  | 2 / 74 (2.70%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 1 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Pneumonitis                                     | Additional description: Pneumonitis                         |                |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)  | 2 / 74 (2.70%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 2 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Pneumothorax                                    | Additional description: Pneumothorax                        |                |  |
| subjects affected / exposed                     | 2 / 75 (2.67%)  | 0 / 74 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2   | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Psychiatric disorders                           |   |                |  |
| Depression                                      | Additional description: Depression                          |                |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)  | 1 / 74 (1.35%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Investigations                                  |   |                |  |
| Alanine aminotransferase increased              | Additional description: Alanine aminotransferase increased  |                |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)  | 1 / 74 (1.35%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Aspartate aminotransferase abnormal             | Additional description: Aspartate aminotransferase abnormal |                |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)  | 1 / 74 (1.35%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Weight decreased                                | Additional description: Weight decreased                    |                |  |

|   |   |                |  |
|---|---|----------------|--|
| subjects affected / exposed                     | 1 / 75 (1.33%)  | 0 / 74 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2   | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Injury, poisoning and procedural complications  |   |                |  |
| Femoral neck fracture                           | Additional description: Femoral neck fracture         |                |  |
| subjects affected / exposed                     | 1 / 75 (1.33%)  | 0 / 74 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Congenital, familial and genetic disorders      |   |                |  |
| Aplasia   | Additional description: Aplasia                       |                |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)  | 1 / 74 (1.35%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Cardiac disorders                               |   |                |  |
| Cardiogenic shock                               | Additional description: Cardiogenic shock             |                |  |
| subjects affected / exposed                     | 1 / 75 (1.33%)  | 0 / 74 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1   | 0 / 0          |  |
| deaths causally related to treatment / all      | 1 / 1   | 0 / 0          |  |
| Cardiac failure                                 | Additional description: Cardiac failure               |                |  |
| subjects affected / exposed                     | 2 / 75 (2.67%)  | 1 / 74 (1.35%) |  |
| occurrences causally related to treatment / all | 2 / 2   | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Cardiotoxicity                                  | Additional description: Cardiotoxicity                |                |  |
| subjects affected / exposed                     | 1 / 75 (1.33%)  | 0 / 74 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1   | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Left ventricular dysfunction                    | Additional description: Left ventricular dysfunction  |                |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)  | 2 / 74 (2.70%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 2 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Nervous system disorders                        |   |                |  |
| Central nervous system lesion                   | Additional description: Central nervous system lesion |                |  |

|   |  |                  |  |
|---|--|------------------|--|
| subjects affected / exposed                     | 0 / 75 (0.00%)                                   | 1 / 74 (1.35%)   |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Dementia  | Additional description: Dementia                 |                  |  |
| subjects affected / exposed                     | 1 / 75 (1.33%)                                   | 0 / 74 (0.00%)   |  |
| occurrences causally related to treatment / all | 1 / 1  | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Haemorrhage intracranial                        | Additional description: Haemorrhage intracranial |                  |  |
| subjects affected / exposed                     | 1 / 75 (1.33%)                                   | 0 / 74 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Blood and lymphatic system disorders            |  |                  |  |
| Anaemia   | Additional description: Anaemia                  |                  |  |
| subjects affected / exposed                     | 2 / 75 (2.67%)                                   | 3 / 74 (4.05%)   |  |
| occurrences causally related to treatment / all | 2 / 2  | 3 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Febrile neutropenia                             | Additional description: Febrile neutropenia      |                  |  |
| subjects affected / exposed                     | 3 / 75 (4.00%)                                   | 13 / 74 (17.57%) |  |
| occurrences causally related to treatment / all | 3 / 3  | 13 / 13          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Leukopenia                                      | Additional description: Leukopenia               |                  |  |
| subjects affected / exposed                     | 1 / 75 (1.33%)                                   | 1 / 74 (1.35%)   |  |
| occurrences causally related to treatment / all | 1 / 1  | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Lymphopenia                                     | Additional description: Lymphopenia              |                  |  |
| subjects affected / exposed                     | 1 / 75 (1.33%)                                   | 0 / 74 (0.00%)   |  |
| occurrences causally related to treatment / all | 1 / 1  | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Neutropenia                                     | Additional description: Neutropenia              |                  |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)                                   | 10 / 74 (13.51%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 14 / 14          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Pancytopenia                                    | Additional description: Pancytopenia             |                  |  |

|   |   |                |  |
|---|---|----------------|--|
| subjects affected / exposed                     | 1 / 75 (1.33%)                                  | 0 / 74 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1   | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Thrombocytopenia                                | Additional description: Thrombocytopenia        |                |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)                                  | 6 / 74 (8.11%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 7 / 7          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Gastrointestinal disorders                      |   |                |  |
| Abdominal pain                                  | Additional description: Abdominal pain          |                |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)                                  | 2 / 74 (2.70%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Constipation                                    | Additional description: Constipation            |                |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)                                  | 1 / 74 (1.35%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Diarrhoea                                       | Additional description: Diarrhoea               |                |  |
| subjects affected / exposed                     | 1 / 75 (1.33%)                                  | 0 / 74 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Faecaloma                                       | Additional description: Faecaloma               |                |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)                                  | 1 / 74 (1.35%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Enteritis                                       | Additional description: Enteritis               |                |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)                                  | 1 / 74 (1.35%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Oesophageal ulcer                               | Additional description: Oesophageal ulcer       |                |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)                                  | 1 / 74 (1.35%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Oesophagitis ulcerative                         | Additional description: Oesophagitis ulcerative |                |  |

|   |  |                |  |
|---|--|----------------|--|
| subjects affected / exposed                     | 1 / 75 (1.33%)                                   | 0 / 74 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| Subileus  | Additional description: Subileus                 |                |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)                                   | 2 / 74 (2.70%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| Vomiting  | Additional description: Vomiting                 |                |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)                                   | 1 / 74 (1.35%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| Renal and urinary disorders                     |  |                |  |
| Renal failure                                   | Additional description: Renal failure            |                |  |
| subjects affected / exposed                     | 1 / 75 (1.33%)                                   | 0 / 74 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| Musculoskeletal and connective tissue disorders |  |                |  |
| Groin pain                                      | Additional description: Groin pain               |                |  |
| subjects affected / exposed                     | 1 / 75 (1.33%)                                   | 0 / 74 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| Infections and infestations                     |  |                |  |
| Device related infection                        | Additional description: Device related infection |                |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)                                   | 2 / 74 (2.70%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| Intervertebral discitis                         | Additional description: Intervertebral discitis  |                |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)                                   | 1 / 74 (1.35%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| Infection                                       | Additional description: Infection                |                |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)                                   | 1 / 74 (1.35%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |



|                                    |   |                |                |
|------------------------------------|---|----------------|----------------|
| Pneumococcal sepsis                | Additional description: Pneumococcal sepsis     |                |                |
|                                    | subjects affected / exposed                     | 1 / 75 (1.33%) | 0 / 74 (0.00%) |
|                                    | occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |
|                                    | deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |
| Pneumonia pneumococcal             | Additional description: Pneumonia pneumococcal  |                |                |
|                                    | subjects affected / exposed                     | 1 / 75 (1.33%) | 0 / 74 (0.00%) |
|                                    | occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |
|                                    | deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |
| Pneumonia                          | Additional description: Pneumonia               |                |                |
|                                    | subjects affected / exposed                     | 2 / 75 (2.67%) | 1 / 74 (1.35%) |
|                                    | occurrences causally related to treatment / all | 1 / 3          | 1 / 1          |
|                                    | deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |
| Pyelonephritis                     | Additional description: Pyelonephritis          |                |                |
|                                    | subjects affected / exposed                     | 1 / 75 (1.33%) | 2 / 74 (2.70%) |
|                                    | occurrences causally related to treatment / all | 1 / 1          | 1 / 2          |
|                                    | deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |
| Septic shock                       | Additional description: Septic shock            |                |                |
|                                    | subjects affected / exposed                     | 0 / 75 (0.00%) | 2 / 74 (2.70%) |
|                                    | occurrences causally related to treatment / all | 0 / 0          | 2 / 2          |
|                                    | deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |
| Sepsis                             | Additional description: Sepsis                  |                |                |
|                                    | subjects affected / exposed                     | 1 / 75 (1.33%) | 0 / 74 (0.00%) |
|                                    | occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |
|                                    | deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |
| Urinary tract infection            | Additional description: Urinary tract infection |                |                |
|                                    | subjects affected / exposed                     | 1 / 75 (1.33%) | 0 / 74 (0.00%) |
|                                    | occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |
|                                    | deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders |   |                |                |
|                                    | Additional description: Cell death              |                |                |
|                                    | subjects affected / exposed                     | 0 / 75 (0.00%) | 1 / 74 (1.35%) |
|                                    | occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |
|                                    | deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |

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

| Non-serious adverse events  | ARM A   | ARM B             |  |
|---|---|-------------------|--|
| Total subjects affected by non-serious adverse events               |   |                   |  |
| subjects affected / exposed   | 75 / 75 (100.00%)                                   | 74 / 74 (100.00%) |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |                   |  |
| Papilloma   | Additional description: Papilloma                   |                   |  |
| subjects affected / exposed   | 0 / 75 (0.00%)                                      | 1 / 74 (1.35%)    |  |
| occurrences (all)   | 0   | 1                 |  |
| Vascular disorders  |   |                   |  |
| Deep vein thrombosis  | Additional description: Deep vein thrombosis        |                   |  |
| subjects affected / exposed   | 1 / 75 (1.33%)                                      | 3 / 74 (4.05%)    |  |
| occurrences (all)   | 14  | 35                |  |
| Flushing  | Additional description: Flushing                    |                   |  |
| subjects affected / exposed   | 3 / 75 (4.00%)                                      | 2 / 74 (2.70%)    |  |
| occurrences (all)   | 12  | 13                |  |
| Hot flush   | Additional description: Hot flush                   |                   |  |
| subjects affected / exposed   | 1 / 75 (1.33%)                                      | 1 / 74 (1.35%)    |  |
| occurrences (all)   | 2   | 1                 |  |
| Hypertension  | Additional description: Hypertension                |                   |  |
| subjects affected / exposed   | 1 / 75 (1.33%)                                      | 0 / 74 (0.00%)    |  |
| occurrences (all)   | 1   | 0                 |  |
| Hypotension   | Additional description: Hypotension                 |                   |  |
| subjects affected / exposed   | 0 / 75 (0.00%)                                      | 1 / 74 (1.35%)    |  |
| occurrences (all)   | 0   | 1                 |  |
| Jugular vein thrombosis   | Additional description: Jugular vein thrombosis     |                   |  |
| subjects affected / exposed   | 1 / 75 (1.33%)                                      | 0 / 74 (0.00%)    |  |
| occurrences (all)   | 2   | 0                 |  |
| Lymphoedema   | Additional description: Lymphoedema                 |                   |  |
| subjects affected / exposed   | 0 / 75 (0.00%)                                      | 1 / 74 (1.35%)    |  |
| occurrences (all)   | 0   | 3                 |  |
| Pallor  | Additional description: Pallor                      |                   |  |
| subjects affected / exposed   | 1 / 75 (1.33%)                                      | 0 / 74 (0.00%)    |  |
| occurrences (all)   | 1   | 0                 |  |
| Superficial vein thrombosis   | Additional description: Superficial vein thrombosis |                   |  |

|  |   |                |  |
|--|---|----------------|--|
| subjects affected / exposed                          | 1 / 75 (1.33%)                                    | 1 / 74 (1.35%) |  |
| occurrences (all)                                    | 1   | 1              |  |
| Thrombophlebitis                                     | Additional description: Thrombophlebitis          |                |  |
| subjects affected / exposed                          | 0 / 75 (0.00%)                                    | 1 / 74 (1.35%) |  |
| occurrences (all)                                    | 0   | 1              |  |
| Vascular pain  | Additional description: Vascular pain             |                |  |
| subjects affected / exposed                          | 1 / 75 (1.33%)                                    | 0 / 74 (0.00%) |  |
| occurrences (all)                                    | 1   | 0              |  |
| Vena cava thrombosis                                 | Additional description: Vena cava thrombosis      |                |  |
| subjects affected / exposed                          | 0 / 75 (0.00%)                                    | 1 / 74 (1.35%) |  |
| occurrences (all)                                    | 0   | 8              |  |
| Venous thrombosis                                    | Additional description: Venous thrombosis         |                |  |
| subjects affected / exposed                          | 1 / 75 (1.33%)                                    | 2 / 74 (2.70%) |  |
| occurrences (all)                                    | 1   | 4              |  |
| Surgical and medical procedures                      |   |                |  |
| Manual lymphatic drainage                            | Additional description: Manual lymphatic drainage |                |  |
| subjects affected / exposed                          | 1 / 75 (1.33%)                                    | 0 / 74 (0.00%) |  |
| occurrences (all)                                    | 2   | 0              |  |
| General disorders and administration site conditions |   |                |  |
| Asthenia   | Additional description: Asthenia                  |                |  |
| subjects affected / exposed                          | 2 / 75 (2.67%)                                    | 6 / 74 (8.11%) |  |
| occurrences (all)                                    | 2   | 11             |  |
| Catheter site oedema                                 | Additional description: Catheter site oedema      |                |  |
| subjects affected / exposed                          | 0 / 75 (0.00%)                                    | 1 / 74 (1.35%) |  |
| occurrences (all)                                    | 0   | 1              |  |
| Chest discomfort                                     | Additional description: Chest discomfort          |                |  |
| subjects affected / exposed                          | 1 / 75 (1.33%)                                    | 0 / 74 (0.00%) |  |
| occurrences (all)                                    | 1   | 0              |  |
| Chest pain   | Additional description: Chest pain                |                |  |
| subjects affected / exposed                          | 3 / 75 (4.00%)                                    | 4 / 74 (5.41%) |  |
| occurrences (all)                                    | 7   | 5              |  |
| Chills   | Additional description: Chills                    |                |  |
| subjects affected / exposed                          | 0 / 75 (0.00%)                                    | 2 / 74 (2.70%) |  |
| occurrences (all)                                    | 0   | 4              |  |
| Discomfort   | Additional description: Discomfort                |                |  |

|                                       |   |                  |  |
|---------------------------------------|---|------------------|--|
| subjects affected / exposed           | 0 / 75 (0.00%)  | 1 / 74 (1.35%)   |  |
| occurrences (all)                     | 0   | 10               |  |
| Face oedema                           | Additional description: Face oedema                           |                  |  |
| subjects affected / exposed           | 0 / 75 (0.00%)  | 1 / 74 (1.35%)   |  |
| occurrences (all)                     | 0   | 1                |  |
| Fatigue                               | Additional description: Fatigue                               |                  |  |
| subjects affected / exposed           | 52 / 75 (69.33%)  | 66 / 74 (89.19%) |  |
| occurrences (all)                     | 174   | 451              |  |
| Facial pain                           | Additional description: Facial pain                           |                  |  |
| subjects affected / exposed           | 0 / 75 (0.00%)  | 1 / 74 (1.35%)   |  |
| occurrences (all)                     | 0   | 2                |  |
| General physical health deterioration | Additional description: General physical health deterioration |                  |  |
| subjects affected / exposed           | 1 / 75 (1.33%)  | 2 / 74 (2.70%)   |  |
| occurrences (all)                     | 2   | 2                |  |
| Inflammation                          | Additional description: Inflammation                          |                  |  |
| subjects affected / exposed           | 1 / 75 (1.33%)  | 1 / 74 (1.35%)   |  |
| occurrences (all)                     | 2   | 1                |  |
| Influenza like illness                | Additional description: Influenza like illness                |                  |  |
| subjects affected / exposed           | 1 / 75 (1.33%)  | 3 / 74 (4.05%)   |  |
| occurrences (all)                     | 1   | 3                |  |
| Medical device site thrombosis        | Additional description: Medical device site thrombosis        |                  |  |
| subjects affected / exposed           | 0 / 75 (0.00%)  | 1 / 74 (1.35%)   |  |
| occurrences (all)                     | 0   | 2                |  |
| Mucosal inflammation                  | Additional description: Mucosal inflammation                  |                  |  |
| subjects affected / exposed           | 26 / 75 (34.67%)  | 30 / 74 (40.54%) |  |
| occurrences (all)                     | 53  | 63               |  |
| Mucosal toxicity                      | Additional description: Mucosal toxicity                      |                  |  |
| subjects affected / exposed           | 1 / 75 (1.33%)  | 0 / 74 (0.00%)   |  |
| occurrences (all)                     | 1   | 0                |  |
| Non-cardiac chest pain                | Additional description: Non-cardiac chest pain                |                  |  |
| subjects affected / exposed           | 1 / 75 (1.33%)  | 1 / 74 (1.35%)   |  |
| occurrences (all)                     | 1   | 1                |  |
| Oedema peripheral                     | Additional description: Oedema peripheral                     |                  |  |
| subjects affected / exposed           | 7 / 75 (9.33%)  | 8 / 74 (10.81%)  |  |
| occurrences (all)                     | 22  | 20               |  |
| Oedema                                | Additional description: Oedema                                |                  |  |

|  |  |                  |  |
|--|--|------------------|--|
| subjects affected / exposed              | 0 / 75 (0.00%)   | 3 / 74 (4.05%)   |  |
| occurrences (all)                        | 0  | 5                |  |
| Pain                                     | Additional description: Pain                           |                  |  |
| subjects affected / exposed              | 5 / 75 (6.67%)   | 12 / 74 (16.22%) |  |
| occurrences (all)                        | 11   | 30               |  |
| Pyrexia                                  | Additional description: Pyrexia                        |                  |  |
| subjects affected / exposed              | 7 / 75 (9.33%)   | 18 / 74 (24.32%) |  |
| occurrences (all)                        | 9  | 24               |  |
| Unevaluable event                        | Additional description: Unevaluable event              |                  |  |
| subjects affected / exposed              | 1 / 75 (1.33%)   | 2 / 74 (2.70%)   |  |
| occurrences (all)                        | 1  | 2                |  |
| Xerosis                                  | Additional description: Xerosis                        |                  |  |
| subjects affected / exposed              | 2 / 75 (2.67%)   | 3 / 74 (4.05%)   |  |
| occurrences (all)                        | 5  | 4                |  |
| Reproductive system and breast disorders |  |                  |  |
| Breast pain                              | Additional description: Breast pain                    |                  |  |
| subjects affected / exposed              | 1 / 75 (1.33%)   | 0 / 74 (0.00%)   |  |
| occurrences (all)                        | 1  | 0                |  |
| Gynaecomastia                            | Additional description: Gynaecomastia                  |                  |  |
| subjects affected / exposed              | 1 / 75 (1.33%)   | 0 / 74 (0.00%)   |  |
| occurrences (all)                        | 1  | 0                |  |
| Intermenstrual bleeding                  | Additional description: Intermenstrual bleeding        |                  |  |
| subjects affected / exposed              | 0 / 75 (0.00%)   | 1 / 74 (1.35%)   |  |
| occurrences (all)                        | 0  | 5                |  |
| Pelvic pain                              | Additional description: Pelvic pain                    |                  |  |
| subjects affected / exposed              | 1 / 75 (1.33%)   | 1 / 74 (1.35%)   |  |
| occurrences (all)                        | 3  | 1                |  |
| Vaginal haemorrhage                      | Additional description: Vaginal haemorrhage            |                  |  |
| subjects affected / exposed              | 1 / 75 (1.33%)   | 1 / 74 (1.35%)   |  |
| occurrences (all)                        | 1  | 1                |  |
| Vulvovaginal burning sensation           | Additional description: Vulvovaginal burning sensation |                  |  |
| subjects affected / exposed              | 1 / 75 (1.33%)   | 0 / 74 (0.00%)   |  |
| occurrences (all)                        | 1  | 0                |  |
| Vulvovaginal dryness                     | Additional description: Vulvovaginal dryness           |                  |  |

|   |   |                  |  |
|---|---|------------------|--|
| subjects affected / exposed                     | 1 / 75 (1.33%)                              | 0 / 74 (0.00%)   |  |
| occurrences (all)                               | 1   | 0                |  |
| Respiratory, thoracic and mediastinal disorders |   |                  |  |
| Cough   | Additional description: Cough               |                  |  |
| subjects affected / exposed                     | 15 / 75 (20.00%)                            | 15 / 74 (20.27%) |  |
| occurrences (all)                               | 28  | 23               |  |
| Dysphonia                                       | Additional description: Dysphonia           |                  |  |
| subjects affected / exposed                     | 1 / 75 (1.33%)                              | 0 / 74 (0.00%)   |  |
| occurrences (all)                               | 1   | 0                |  |
| Dyspnoea  | Additional description: Dyspnoea            |                  |  |
| subjects affected / exposed                     | 9 / 75 (12.00%)                             | 13 / 74 (17.57%) |  |
| occurrences (all)                               | 15  | 46               |  |
| Dyspnoea exertional                             | Additional description: Dyspnoea exertional |                  |  |
| subjects affected / exposed                     | 1 / 75 (1.33%)                              | 5 / 74 (6.76%)   |  |
| occurrences (all)                               | 2   | 42               |  |
| Epistaxis                                       | Additional description: Epistaxis           |                  |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)                              | 3 / 74 (4.05%)   |  |
| occurrences (all)                               | 0   | 3                |  |
| Haemoptysis                                     | Additional description: Haemoptysis         |                  |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)                              | 1 / 74 (1.35%)   |  |
| occurrences (all)                               | 0   | 13               |  |
| Hiccups   | Additional description: Hiccups             |                  |  |
| subjects affected / exposed                     | 1 / 75 (1.33%)                              | 3 / 74 (4.05%)   |  |
| occurrences (all)                               | 1   | 4                |  |
| Lung disorder                                   | Additional description: Lung disorder       |                  |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)                              | 1 / 74 (1.35%)   |  |
| occurrences (all)                               | 0   | 1                |  |
| Nasal congestion                                | Additional description: Nasal congestion    |                  |  |
| subjects affected / exposed                     | 1 / 75 (1.33%)                              | 0 / 74 (0.00%)   |  |
| occurrences (all)                               | 1   | 0                |  |
| Oropharyngeal pain                              | Additional description: Oropharyngeal pain  |                  |  |
| subjects affected / exposed                     | 1 / 75 (1.33%)                              | 1 / 74 (1.35%)   |  |
| occurrences (all)                               | 1   | 1                |  |
| Pleural disorder                                | Additional description: Pleural disorder    |                  |  |

|  |   |                         |  |
|--|---|-------------------------|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 75 (0.00%)<br>0   | 1 / 74 (1.35%)<br>1     |  |
| Pulmonary embolism                               | Additional description: Pulmonary embolism                  |                         |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 75 (1.33%)<br>1   | 0 / 74 (0.00%)<br>0     |  |
| Productive cough                                 | Additional description: Productive cough                    |                         |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 75 (0.00%)<br>0   | 2 / 74 (2.70%)<br>3     |  |
| Rhinitis allergic                                | Additional description: Rhinitis allergic                   |                         |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 75 (0.00%)<br>0   | 1 / 74 (1.35%)<br>1     |  |
| Rhinorrhoea                                      | Additional description: Rhinorrhoea                         |                         |  |
| subjects affected / exposed<br>occurrences (all) | 2 / 75 (2.67%)<br>3   | 4 / 74 (5.41%)<br>5     |  |
| Psychiatric disorders                            |   |                         |  |
| Anxiety  | Additional description: Anxiety                             |                         |  |
| subjects affected / exposed<br>occurrences (all) | 2 / 75 (2.67%)<br>2   | 6 / 74 (8.11%)<br>12    |  |
| Depressed mood                                   | Additional description: Depressed mood                      |                         |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 75 (0.00%)<br>0   | 1 / 74 (1.35%)<br>1     |  |
| Depression                                       | Additional description: Depression                          |                         |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 75 (0.00%)<br>0   | 2 / 74 (2.70%)<br>5     |  |
| Insomnia   | Additional description: Insomnia                            |                         |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 75 (1.33%)<br>1   | 3 / 74 (4.05%)<br>11    |  |
| Sleep disorder                                   | Additional description: Sleep disorder                      |                         |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 75 (0.00%)<br>0   | 2 / 74 (2.70%)<br>2     |  |
| Investigations                                   |   |                         |  |
| Alanine aminotransferase increased               | Additional description: Alanine aminotransferase increased  |                         |  |
| subjects affected / exposed<br>occurrences (all) | 24 / 75 (32.00%)<br>68                                      | 71 / 74 (95.95%)<br>720 |  |
| Aspartate aminotransferase abnormal              | Additional description: Aspartate aminotransferase abnormal |                         |  |

|  |  |                  |  |
|--|--|------------------|--|
| subjects affected / exposed            | 0 / 75 (0.00%)   | 2 / 74 (2.70%)   |  |
| occurrences (all)                      | 0  | 28               |  |
| Aspartate aminotransferase increased   | Additional description: Aspartate aminotransferase increased   |                  |  |
| subjects affected / exposed            | 20 / 75 (26.67%)   | 61 / 74 (82.43%) |  |
| occurrences (all)                      | 50   | 420              |  |
| Blood bilirubin                        | Additional description: Blood bilirubin                        |                  |  |
| subjects affected / exposed            | 0 / 75 (0.00%)   | 1 / 74 (1.35%)   |  |
| occurrences (all)                      | 0  | 1                |  |
| Blood alkaline phosphatase increased   | Additional description: Blood alkaline phosphatase increased   |                  |  |
| subjects affected / exposed            | 25 / 75 (33.33%)   | 53 / 74 (71.62%) |  |
| occurrences (all)                      | 56   | 544              |  |
| Blood alkaline phosphatase             | Additional description: Blood alkaline phosphatase             |                  |  |
| subjects affected / exposed            | 0 / 75 (0.00%)   | 1 / 74 (1.35%)   |  |
| occurrences (all)                      | 0  | 1                |  |
| Blood bilirubin increased              | Additional description: Blood bilirubin increased              |                  |  |
| subjects affected / exposed            | 7 / 75 (9.33%)   | 37 / 74 (50.00%) |  |
| occurrences (all)                      | 11   | 125              |  |
| Blood creatine phosphokinase           | Additional description: Blood creatine phosphokinase           |                  |  |
| subjects affected / exposed            | 0 / 75 (0.00%)   | 3 / 74 (4.05%)   |  |
| occurrences (all)                      | 0  | 11               |  |
| Blood creatine phosphokinase increased | Additional description: Blood creatine phosphokinase increased |                  |  |
| subjects affected / exposed            | 10 / 75 (13.33%)   | 30 / 74 (40.54%) |  |
| occurrences (all)                      | 14   | 198              |  |
| Blood creatinine                       | Additional description: Blood creatinine                       |                  |  |
| subjects affected / exposed            | 0 / 75 (0.00%)   | 1 / 74 (1.35%)   |  |
| occurrences (all)                      | 0  | 1                |  |
| Blood creatinine increased             | Additional description: Blood creatinine increased             |                  |  |
| subjects affected / exposed            | 11 / 75 (14.67%)   | 29 / 74 (39.19%) |  |
| occurrences (all)                      | 24   | 136              |  |
| Blood lactate dehydrogenase increased  | Additional description: Blood lactate dehydrogenase increased  |                  |  |
| subjects affected / exposed            | 0 / 75 (0.00%)   | 2 / 74 (2.70%)   |  |
| occurrences (all)                      | 0  | 2                |  |
| Blood sodium increased                 | Additional description: Blood sodium increased                 |                  |  |



|                                      |  |                  |  |
|--------------------------------------|--|------------------|--|
| subjects affected / exposed          | 0 / 75 (0.00%)   | 1 / 74 (1.35%)   |  |
| occurrences (all)                    | 0  | 1                |  |
| Blood urea increased                 | Additional description: Blood urea increased                 |                  |  |
| subjects affected / exposed          | 0 / 75 (0.00%)   | 1 / 74 (1.35%)   |  |
| occurrences (all)                    | 0  | 2                |  |
| Cardiac stress test                  | Additional description: Cardiac stress test                  |                  |  |
| subjects affected / exposed          | 0 / 75 (0.00%)   | 1 / 74 (1.35%)   |  |
| occurrences (all)                    | 0  | 1                |  |
| Creatinine renal clearance increased | Additional description: Creatinine renal clearance increased |                  |  |
| subjects affected / exposed          | 0 / 75 (0.00%)   | 1 / 74 (1.35%)   |  |
| occurrences (all)                    | 0  | 1                |  |
| Ejection fraction decreased          | Additional description: Ejection fraction decreased          |                  |  |
| subjects affected / exposed          | 1 / 75 (1.33%)   | 1 / 74 (1.35%)   |  |
| occurrences (all)                    | 1  | 1                |  |
| Gamma-glutamyltransferase increased  | Additional description: Gamma-glutamyltransferase increased  |                  |  |
| subjects affected / exposed          | 2 / 75 (2.67%)   | 16 / 74 (21.62%) |  |
| occurrences (all)                    | 3  | 77               |  |
| Haemoglobin                          | Additional description: Haemoglobin                          |                  |  |
| subjects affected / exposed          | 0 / 75 (0.00%)   | 1 / 74 (1.35%)   |  |
| occurrences (all)                    | 0  | 1                |  |
| Haemoglobin decreased                | Additional description: Haemoglobin decreased                |                  |  |
| subjects affected / exposed          | 0 / 75 (0.00%)   | 1 / 74 (1.35%)   |  |
| occurrences (all)                    | 0  | 1                |  |
| Lymphocyte count                     | Additional description: Lymphocyte count                     |                  |  |
| subjects affected / exposed          | 0 / 75 (0.00%)   | 1 / 74 (1.35%)   |  |
| occurrences (all)                    | 0  | 1                |  |
| Neutrophil count decreased           | Additional description: Neutrophil count decreased           |                  |  |
| subjects affected / exposed          | 0 / 75 (0.00%)   | 3 / 74 (4.05%)   |  |
| occurrences (all)                    | 0  | 5                |  |
| Platelet count decreased             | Additional description: Platelet count decreased             |                  |  |
| subjects affected / exposed          | 0 / 75 (0.00%)   | 3 / 74 (4.05%)   |  |
| occurrences (all)                    | 0  | 8                |  |
| Transaminases                        | Additional description: Transaminases                        |                  |  |
| subjects affected / exposed          | 0 / 75 (0.00%)   | 1 / 74 (1.35%)   |  |
| occurrences (all)                    | 0  | 2                |  |

|  |  |                |  |
|--|--|----------------|--|
| Transaminases increased<br>subjects affected / exposed<br>occurrences (all)          | Additional description: Transaminases increased          |                |  |
|  | 0 / 75 (0.00%)   | 2 / 74 (2.70%) |  |
|  | 0  | 4              |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                 | Additional description: Weight decreased                 |                |  |
|  | 1 / 75 (1.33%)   | 5 / 74 (6.76%) |  |
|  | 5  | 11             |  |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all) | Additional description: White blood cell count decreased |                |  |
|  | 0 / 75 (0.00%)   | 2 / 74 (2.70%) |  |
|  | 0  | 2              |  |
| Injury, poisoning and procedural complications                                       |  |                |  |
|  | Additional description: Ankle fracture                   |                |  |
|  | 0 / 75 (0.00%)   | 1 / 74 (1.35%) |  |
|  | 0  | 1              |  |
|  | Additional description: Bone fissure                     |                |  |
|  | 1 / 75 (1.33%)   | 0 / 74 (0.00%) |  |
|  | 3  | 0              |  |
|  | Additional description: Burn oesophageal                 |                |  |
|  | 0 / 75 (0.00%)   | 1 / 74 (1.35%) |  |
|  | 0  | 1              |  |
|  | Additional description: Tendon injury                    |                |  |
|  | 0 / 75 (0.00%)   | 1 / 74 (1.35%) |  |
|  | 0  | 1              |  |
|  | Additional description: Tooth fracture                   |                |  |
|  | 0 / 75 (0.00%)   | 1 / 74 (1.35%) |  |
|  | 0  | 1              |  |
|  | Additional description: Wound complication               |                |  |
|  | 0 / 75 (0.00%)   | 1 / 74 (1.35%) |  |
|  | 0  | 2              |  |
| Congenital, familial and genetic disorders   |  |                |  |
|  | Additional description: Aplasia                          |                |  |
|  | 1 / 75 (1.33%)   | 0 / 74 (0.00%) |  |
|  | 1  | 0              |  |
| Cardiac disorders  |  |                |  |
|  | Additional description: Atrial fibrillation              |                |  |
|  | 1 / 75 (1.33%)   | 0 / 74 (0.00%) |  |
|  | 3  | 0              |  |

|  |  |                        |
|--|--|------------------------|
| Cardiac dysfunction<br>subjects affected / exposed<br>occurrences (all)    | Additional description: Cardiac dysfunction    |                        |
|  | 0 / 75 (0.00%)<br>0                            | 1 / 74 (1.35%)<br>1    |
| Cardiac failure<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Cardiac failure        |                        |
|  | 1 / 75 (1.33%)<br>2                            | 3 / 74 (4.05%)<br>3    |
| Extrasystoles<br>subjects affected / exposed<br>occurrences (all)          | Additional description: Extrasystoles          |                        |
|  | 1 / 75 (1.33%)<br>2                            | 0 / 74 (0.00%)<br>0    |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Palpitations           |                        |
|  | 1 / 75 (1.33%)<br>1                            | 0 / 74 (0.00%)<br>0    |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Tachycardia            |                        |
|  | 2 / 75 (2.67%)<br>2                            | 0 / 74 (0.00%)<br>0    |
| Nervous system disorders   |  |                        |
|  | Additional description: Burning sensation      |                        |
| Burning sensation<br>subjects affected / exposed<br>occurrences (all)      | 1 / 75 (1.33%)<br>2                            | 1 / 74 (1.35%)<br>1    |
| Carpal tunnel syndrome<br>subjects affected / exposed<br>occurrences (all) | Additional description: Carpal tunnel syndrome |                        |
|  | 0 / 75 (0.00%)<br>0                            | 2 / 74 (2.70%)<br>6    |
| Dementia<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Dementia               |                        |
|  | 1 / 75 (1.33%)<br>2                            | 0 / 74 (0.00%)<br>0    |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Dizziness              |                        |
|  | 0 / 75 (0.00%)<br>0                            | 1 / 74 (1.35%)<br>3    |
| Dysaesthesia<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Dysaesthesia           |                        |
|  | 0 / 75 (0.00%)<br>0                            | 2 / 74 (2.70%)<br>2    |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Dysgeusia              |                        |
|  | 11 / 75 (14.67%)<br>18                         | 10 / 74 (13.51%)<br>41 |
| Headache   | Additional description: Headache               |                        |
|  |  |                        |

|                                      |   |                |  |
|--------------------------------------|---|----------------|--|
| subjects affected / exposed          | 8 / 75 (10.67%)                               | 6 / 74 (8.11%) |  |
| occurrences (all)                    | 11  | 7              |  |
| Hemiparesis                          | Additional description: Hemiparesis           |                |  |
| subjects affected / exposed          | 0 / 75 (0.00%)                                | 1 / 74 (1.35%) |  |
| occurrences (all)                    | 0   | 1              |  |
| Hypoaesthesia                        | Additional description: Hypoaesthesia         |                |  |
| subjects affected / exposed          | 0 / 75 (0.00%)                                | 1 / 74 (1.35%) |  |
| occurrences (all)                    | 0   | 1              |  |
| Hypokinesia                          | Additional description: Hypokinesia           |                |  |
| subjects affected / exposed          | 0 / 75 (0.00%)                                | 1 / 74 (1.35%) |  |
| occurrences (all)                    | 0   | 1              |  |
| Memory impairment                    | Additional description: Memory impairment     |                |  |
| subjects affected / exposed          | 0 / 75 (0.00%)                                | 1 / 74 (1.35%) |  |
| occurrences (all)                    | 0   | 1              |  |
| Migraine                             | Additional description: Migraine              |                |  |
| subjects affected / exposed          | 1 / 75 (1.33%)                                | 0 / 74 (0.00%) |  |
| occurrences (all)                    | 1   | 0              |  |
| Neuropathy peripheral                | Additional description: Neuropathy peripheral |                |  |
| subjects affected / exposed          | 0 / 75 (0.00%)                                | 4 / 74 (5.41%) |  |
| occurrences (all)                    | 0   | 9              |  |
| Neuralgia                            | Additional description: Neuralgia             |                |  |
| subjects affected / exposed          | 1 / 75 (1.33%)                                | 0 / 74 (0.00%) |  |
| occurrences (all)                    | 1   | 0              |  |
| Paraesthesia                         | Additional description: Paraesthesia          |                |  |
| subjects affected / exposed          | 2 / 75 (2.67%)                                | 6 / 74 (8.11%) |  |
| occurrences (all)                    | 4   | 22             |  |
| Presyncope                           | Additional description: Presyncope            |                |  |
| subjects affected / exposed          | 0 / 75 (0.00%)                                | 1 / 74 (1.35%) |  |
| occurrences (all)                    | 0   | 1              |  |
| Sciatica                             | Additional description: Sciatica              |                |  |
| subjects affected / exposed          | 2 / 75 (2.67%)                                | 2 / 74 (2.70%) |  |
| occurrences (all)                    | 7   | 5              |  |
| Taste disorder                       | Additional description: Taste disorder        |                |  |
| subjects affected / exposed          | 0 / 75 (0.00%)                                | 1 / 74 (1.35%) |  |
| occurrences (all)                    | 0   | 1              |  |
| Blood and lymphatic system disorders |   |                |  |

|                             |   |                   |
|-----------------------------|---|-------------------|
| Anaemia                     | Additional description: Anaemia             |                   |
|                             | 65 / 75 (86.67%)                            | 74 / 74 (100.00%) |
| subjects affected / exposed | 315   | 1555              |
| occurrences (all)           |   |                   |
| Febrile neutropenia         | Additional description: Febrile neutropenia |                   |
|                             | 7 / 75 (9.33%)                              | 10 / 74 (13.51%)  |
| subjects affected / exposed | 8   | 15                |
| occurrences (all)           |   |                   |
| Hyperleukocytosis           | Additional description: Hyperleukocytosis   |                   |
|                             | 0 / 75 (0.00%)                              | 1 / 74 (1.35%)    |
| subjects affected / exposed | 0   | 1                 |
| occurrences (all)           |   |                   |
| Leukopenia                  | Additional description: Leukopenia          |                   |
|                             | 31 / 75 (41.33%)                            | 66 / 74 (89.19%)  |
| subjects affected / exposed | 91  | 908               |
| occurrences (all)           |   |                   |
| Lymphopenia                 | Additional description: Lymphopenia         |                   |
|                             | 4 / 75 (5.33%)                              | 8 / 74 (10.81%)   |
| subjects affected / exposed | 6   | 22                |
| occurrences (all)           |   |                   |
| Neutropenia                 | Additional description: Neutropenia         |                   |
|                             | 33 / 75 (44.00%)                            | 64 / 74 (86.49%)  |
| subjects affected / exposed | 71  | 739               |
| occurrences (all)           |   |                   |
| Pancytopenia                | Additional description: Pancytopenia        |                   |
|                             | 0 / 75 (0.00%)                              | 1 / 74 (1.35%)    |
| subjects affected / exposed | 0   | 1                 |
| occurrences (all)           |   |                   |
| Thrombocytopenia            | Additional description: Thrombocytopenia    |                   |
|                             | 11 / 75 (14.67%)                            | 60 / 74 (81.08%)  |
| subjects affected / exposed | 20  | 759               |
| occurrences (all)           |   |                   |
| Ear and labyrinth disorders |   |                   |
|                             |   |                   |
| Deafness bilateral          | Additional description: Deafness bilateral  |                   |
|                             | 0 / 75 (0.00%)                              | 1 / 74 (1.35%)    |
| subjects affected / exposed | 0   | 4                 |
| occurrences (all)           |   |                   |
| Ear pain                    | Additional description: Ear pain            |                   |
|                             | 1 / 75 (1.33%)                              | 0 / 74 (0.00%)    |
| subjects affected / exposed | 1   | 0                 |
| occurrences (all)           |   |                   |
| Tinnitus                    | Additional description: Tinnitus            |                   |
|                             | 0 / 75 (0.00%)                              | 1 / 74 (1.35%)    |
| subjects affected / exposed | 0   | 7                 |
| occurrences (all)           |   |                   |
| Vertigo                     | Additional description: Vertigo             |                   |
|                             |   |                   |

|                                  |  |                  |  |
|----------------------------------|--|------------------|--|
| subjects affected / exposed      | 3 / 75 (4.00%)   | 5 / 74 (6.76%)   |  |
| occurrences (all)                | 5  | 11               |  |
| Eye disorders                    |  |                  |  |
| Age-related macular degeneration | Additional description: Age-related macular degeneration |                  |  |
| subjects affected / exposed      | 0 / 75 (0.00%)   | 1 / 74 (1.35%)   |  |
| occurrences (all)                | 0  | 18               |  |
| Cataract                         | Additional description: Cataract                         |                  |  |
| subjects affected / exposed      | 0 / 75 (0.00%)   | 1 / 74 (1.35%)   |  |
| occurrences (all)                | 0  | 1                |  |
| Dry eye                          | Additional description: Dry eye                          |                  |  |
| subjects affected / exposed      | 3 / 75 (4.00%)   | 4 / 74 (5.41%)   |  |
| occurrences (all)                | 3  | 7                |  |
| Eye disorder                     | Additional description: Eye disorder                     |                  |  |
| subjects affected / exposed      | 0 / 75 (0.00%)   | 1 / 74 (1.35%)   |  |
| occurrences (all)                | 0  | 1                |  |
| Lacrimation increased            | Additional description: Lacrimation increased            |                  |  |
| subjects affected / exposed      | 0 / 75 (0.00%)   | 2 / 74 (2.70%)   |  |
| occurrences (all)                | 0  | 2                |  |
| Ocular discomfort                | Additional description: Ocular discomfort                |                  |  |
| subjects affected / exposed      | 1 / 75 (1.33%)   | 0 / 74 (0.00%)   |  |
| occurrences (all)                | 1  | 0                |  |
| Noninfective conjunctivitis      | Additional description: Noninfective conjunctivitis      |                  |  |
| subjects affected / exposed      | 1 / 75 (1.33%)   | 0 / 74 (0.00%)   |  |
| occurrences (all)                | 1  | 0                |  |
| Visual acuity reduced            | Additional description: Visual acuity reduced            |                  |  |
| subjects affected / exposed      | 0 / 75 (0.00%)   | 1 / 74 (1.35%)   |  |
| occurrences (all)                | 0  | 8                |  |
| Xerophthalmia                    | Additional description: Xerophthalmia                    |                  |  |
| subjects affected / exposed      | 1 / 75 (1.33%)   | 0 / 74 (0.00%)   |  |
| occurrences (all)                | 4  | 0                |  |
| Gastrointestinal disorders       |  |                  |  |
| Abdominal pain                   | Additional description: Abdominal pain                   |                  |  |
| subjects affected / exposed      | 2 / 75 (2.67%)   | 15 / 74 (20.27%) |  |
| occurrences (all)                | 3  | 24               |  |
| Abdominal discomfort             | Additional description: Abdominal discomfort             |                  |  |

|                             |  |                  |  |
|-----------------------------|--|------------------|--|
| subjects affected / exposed | 1 / 75 (1.33%)                               | 2 / 74 (2.70%)   |  |
| occurrences (all)           | 1  | 4                |  |
| Abdominal pain lower        | Additional description: Abdominal pain lower |                  |  |
| subjects affected / exposed | 0 / 75 (0.00%)                               | 2 / 74 (2.70%)   |  |
| occurrences (all)           | 0  | 3                |  |
| Abdominal pain upper        | Additional description: Abdominal pain upper |                  |  |
| subjects affected / exposed | 8 / 75 (10.67%)                              | 4 / 74 (5.41%)   |  |
| occurrences (all)           | 19   | 4                |  |
| Abdominal tenderness        | Additional description: Abdominal tenderness |                  |  |
| subjects affected / exposed | 1 / 75 (1.33%)                               | 1 / 74 (1.35%)   |  |
| occurrences (all)           | 1  | 1                |  |
| Aerophagia                  | Additional description: Aerophagia           |                  |  |
| subjects affected / exposed | 1 / 75 (1.33%)                               | 0 / 74 (0.00%)   |  |
| occurrences (all)           | 1  | 0                |  |
| Anal incontinence           | Additional description: Anal incontinence    |                  |  |
| subjects affected / exposed | 0 / 75 (0.00%)                               | 1 / 74 (1.35%)   |  |
| occurrences (all)           | 0  | 1                |  |
| Aphthous ulcer              | Additional description: Aphthous ulcer       |                  |  |
| subjects affected / exposed | 6 / 75 (8.00%)                               | 0 / 74 (0.00%)   |  |
| occurrences (all)           | 14   | 0                |  |
| Ascites                     | Additional description: Ascites              |                  |  |
| subjects affected / exposed | 0 / 75 (0.00%)                               | 1 / 74 (1.35%)   |  |
| occurrences (all)           | 0  | 1                |  |
| Constipation                | Additional description: Constipation         |                  |  |
| subjects affected / exposed | 18 / 75 (24.00%)                             | 28 / 74 (37.84%) |  |
| occurrences (all)           | 35   | 105              |  |
| Colitis                     | Additional description: Colitis              |                  |  |
| subjects affected / exposed | 1 / 75 (1.33%)                               | 0 / 74 (0.00%)   |  |
| occurrences (all)           | 1  | 0                |  |
| Diarrhoea                   | Additional description: Diarrhoea            |                  |  |
| subjects affected / exposed | 11 / 75 (14.67%)                             | 28 / 74 (37.84%) |  |
| occurrences (all)           | 27   | 72               |  |
| Dry mouth                   | Additional description: Dry mouth            |                  |  |
| subjects affected / exposed | 3 / 75 (4.00%)                               | 2 / 74 (2.70%)   |  |
| occurrences (all)           | 14   | 16               |  |
| Dysphagia                   | Additional description: Dysphagia            |                  |  |

|                                    |  |                |  |
|------------------------------------|--|----------------|--|
| subjects affected / exposed        | 2 / 75 (2.67%)   | 0 / 74 (0.00%) |  |
| occurrences (all)                  | 2  | 0              |  |
| Dyschezia                          | Additional description: Dyschezia                          |                |  |
| subjects affected / exposed        | 1 / 75 (1.33%)   | 0 / 74 (0.00%) |  |
| occurrences (all)                  | 1  | 0              |  |
| Dyspepsia                          | Additional description: Dyspepsia                          |                |  |
| subjects affected / exposed        | 5 / 75 (6.67%)   | 7 / 74 (9.46%) |  |
| occurrences (all)                  | 15   | 13             |  |
| Eructation                         | Additional description: Eructation                         |                |  |
| subjects affected / exposed        | 0 / 75 (0.00%)   | 1 / 74 (1.35%) |  |
| occurrences (all)                  | 0  | 1              |  |
| Flatulence                         | Additional description: Flatulence                         |                |  |
| subjects affected / exposed        | 0 / 75 (0.00%)   | 3 / 74 (4.05%) |  |
| occurrences (all)                  | 0  | 7              |  |
| Gastrooesophageal reflux disease   | Additional description: Gastrooesophageal reflux disease   |                |  |
| subjects affected / exposed        | 4 / 75 (5.33%)   | 2 / 74 (2.70%) |  |
| occurrences (all)                  | 7  | 2              |  |
| Gastrointestinal pain              | Additional description: Gastrointestinal pain              |                |  |
| subjects affected / exposed        | 1 / 75 (1.33%)   | 0 / 74 (0.00%) |  |
| occurrences (all)                  | 1  | 0              |  |
| Gastrointestinal motility disorder | Additional description: Gastrointestinal motility disorder |                |  |
| subjects affected / exposed        | 0 / 75 (0.00%)   | 1 / 74 (1.35%) |  |
| occurrences (all)                  | 0  | 1              |  |
| Gingival bleeding                  | Additional description: Gingival bleeding                  |                |  |
| subjects affected / exposed        | 0 / 75 (0.00%)   | 1 / 74 (1.35%) |  |
| occurrences (all)                  | 0  | 1              |  |
| Haematochezia                      | Additional description: Haematochezia                      |                |  |
| subjects affected / exposed        | 1 / 75 (1.33%)   | 0 / 74 (0.00%) |  |
| occurrences (all)                  | 1  | 0              |  |
| Haemorrhoids                       | Additional description: Haemorrhoids                       |                |  |
| subjects affected / exposed        | 0 / 75 (0.00%)   | 1 / 74 (1.35%) |  |
| occurrences (all)                  | 0  | 1              |  |
| Ileus                              | Additional description: Ileus                              |                |  |
| subjects affected / exposed        | 1 / 75 (1.33%)   | 0 / 74 (0.00%) |  |
| occurrences (all)                  | 1  | 0              |  |
| Mouth ulceration                   | Additional description: Mouth ulceration                   |                |  |



|  |   |                  |  |
|--|---|------------------|--|
| subjects affected / exposed            | 0 / 75 (0.00%)                                  | 1 / 74 (1.35%)   |  |
| occurrences (all)                      | 0   | 1                |  |
| Nausea                                 | Additional description: Nausea                  |                  |  |
| subjects affected / exposed            | 47 / 75 (62.67%)                                | 64 / 74 (86.49%) |  |
| occurrences (all)                      | 133   | 298              |  |
| Oral pain                              | Additional description: Oral pain               |                  |  |
| subjects affected / exposed            | 1 / 75 (1.33%)                                  | 0 / 74 (0.00%)   |  |
| occurrences (all)                      | 4   | 0                |  |
| Rectal haemorrhage                     | Additional description: Rectal haemorrhage      |                  |  |
| subjects affected / exposed            | 1 / 75 (1.33%)                                  | 2 / 74 (2.70%)   |  |
| occurrences (all)                      | 1   | 5                |  |
| Salivary hypersecretion                | Additional description: Salivary hypersecretion |                  |  |
| subjects affected / exposed            | 0 / 75 (0.00%)                                  | 1 / 74 (1.35%)   |  |
| occurrences (all)                      | 0   | 2                |  |
| Stomatitis                             | Additional description: Stomatitis              |                  |  |
| subjects affected / exposed            | 1 / 75 (1.33%)                                  | 2 / 74 (2.70%)   |  |
| occurrences (all)                      | 1   | 2                |  |
| Toothache                              | Additional description: Toothache               |                  |  |
| subjects affected / exposed            | 1 / 75 (1.33%)                                  | 2 / 74 (2.70%)   |  |
| occurrences (all)                      | 1   | 2                |  |
| Vomiting                               | Additional description: Vomiting                |                  |  |
| subjects affected / exposed            | 10 / 75 (13.33%)                                | 43 / 74 (58.11%) |  |
| occurrences (all)                      | 13  | 91               |  |
| Hepatobiliary disorders                |   |                  |  |
| Cholestasis                            | Additional description: Cholestasis             |                  |  |
| subjects affected / exposed            | 0 / 75 (0.00%)                                  | 4 / 74 (5.41%)   |  |
| occurrences (all)                      | 0   | 6                |  |
| Hepatic cytolysis                      | Additional description: Hepatic cytolysis       |                  |  |
| subjects affected / exposed            | 1 / 75 (1.33%)                                  | 7 / 74 (9.46%)   |  |
| occurrences (all)                      | 7   | 14               |  |
| Liver disorder                         | Additional description: Liver disorder          |                  |  |
| subjects affected / exposed            | 0 / 75 (0.00%)                                  | 1 / 74 (1.35%)   |  |
| occurrences (all)                      | 0   | 1                |  |
| Skin and subcutaneous tissue disorders |   |                  |  |
| Alopecia                               | Additional description: Alopecia                |                  |  |

|                             |   |                  |  |
|-----------------------------|---|------------------|--|
| subjects affected / exposed | 37 / 75 (49.33%)                            | 33 / 74 (44.59%) |  |
| occurrences (all)           | 123   | 154              |  |
| Dermatitis allergic         | Additional description: Dermatitis allergic |                  |  |
| subjects affected / exposed | 1 / 75 (1.33%)                              | 0 / 74 (0.00%)   |  |
| occurrences (all)           | 1   | 0                |  |
| Dry skin                    | Additional description: Dry skin            |                  |  |
| subjects affected / exposed | 3 / 75 (4.00%)                              | 5 / 74 (6.76%)   |  |
| occurrences (all)           | 11  | 9                |  |
| Eczema                      | Additional description: Eczema              |                  |  |
| subjects affected / exposed | 0 / 75 (0.00%)                              | 1 / 74 (1.35%)   |  |
| occurrences (all)           | 0   | 1                |  |
| Hyperhidrosis               | Additional description: Hyperhidrosis       |                  |  |
| subjects affected / exposed | 1 / 75 (1.33%)                              | 0 / 74 (0.00%)   |  |
| occurrences (all)           | 3   | 0                |  |
| Nail discolouration         | Additional description: Nail discolouration |                  |  |
| subjects affected / exposed | 1 / 75 (1.33%)                              | 0 / 74 (0.00%)   |  |
| occurrences (all)           | 3   | 0                |  |
| Nail disorder               | Additional description: Nail disorder       |                  |  |
| subjects affected / exposed | 2 / 75 (2.67%)                              | 3 / 74 (4.05%)   |  |
| occurrences (all)           | 3   | 27               |  |
| Nail dystrophy              | Additional description: Nail dystrophy      |                  |  |
| subjects affected / exposed | 1 / 75 (1.33%)                              | 2 / 74 (2.70%)   |  |
| occurrences (all)           | 1   | 2                |  |
| Nail ridging                | Additional description: Nail ridging        |                  |  |
| subjects affected / exposed | 1 / 75 (1.33%)                              | 0 / 74 (0.00%)   |  |
| occurrences (all)           | 2   | 0                |  |
| Nail toxicity               | Additional description: Nail toxicity       |                  |  |
| subjects affected / exposed | 0 / 75 (0.00%)                              | 1 / 74 (1.35%)   |  |
| occurrences (all)           | 0   | 1                |  |
| Onychalgia                  | Additional description: Onychalgia          |                  |  |
| subjects affected / exposed | 1 / 75 (1.33%)                              | 0 / 74 (0.00%)   |  |
| occurrences (all)           | 3   | 0                |  |
| Onycholysis                 | Additional description: Onycholysis         |                  |  |
| subjects affected / exposed | 1 / 75 (1.33%)                              | 2 / 74 (2.70%)   |  |
| occurrences (all)           | 3   | 4                |  |
| Onychoclasia                | Additional description: Onychoclasia        |                  |  |

|   |   |                |  |
|---|---|----------------|--|
| subjects affected / exposed                 | 0 / 75 (0.00%)  | 2 / 74 (2.70%) |  |
| occurrences (all)                           | 0   | 3              |  |
| Onychomadesis                               | Additional description: Onychomadesis                               |                |  |
| subjects affected / exposed                 | 0 / 75 (0.00%)  | 1 / 74 (1.35%) |  |
| occurrences (all)                           | 0   | 2              |  |
| Palmar-plantar erythrodysaesthesia syndrome | Additional description: Palmar-plantar erythrodysaesthesia syndrome |                |  |
| subjects affected / exposed                 | 1 / 75 (1.33%)  | 1 / 74 (1.35%) |  |
| occurrences (all)                           | 3   | 2              |  |
| Pruritus                                    | Additional description: Pruritus                                    |                |  |
| subjects affected / exposed                 | 1 / 75 (1.33%)  | 5 / 74 (6.76%) |  |
| occurrences (all)                           | 1   | 16             |  |
| Rash  | Additional description: Rash  |                |  |
| subjects affected / exposed                 | 0 / 75 (0.00%)  | 4 / 74 (5.41%) |  |
| occurrences (all)                           | 0   | 4              |  |
| Rash erythematous                           | Additional description: Rash erythematous                           |                |  |
| subjects affected / exposed                 | 0 / 75 (0.00%)  | 2 / 74 (2.70%) |  |
| occurrences (all)                           | 0   | 6              |  |
| Rash maculo-papular                         | Additional description: Rash maculo-papular                         |                |  |
| subjects affected / exposed                 | 0 / 75 (0.00%)  | 1 / 74 (1.35%) |  |
| occurrences (all)                           | 0   | 2              |  |
| Skin hyperpigmentation                      | Additional description: Skin hyperpigmentation                      |                |  |
| subjects affected / exposed                 | 0 / 75 (0.00%)  | 1 / 74 (1.35%) |  |
| occurrences (all)                           | 0   | 2              |  |
| Skin irritation                             | Additional description: Skin irritation                             |                |  |
| subjects affected / exposed                 | 1 / 75 (1.33%)  | 0 / 74 (0.00%) |  |
| occurrences (all)                           | 1   | 0              |  |
| Renal and urinary disorders                 |   |                |  |
| Acute kidney injury                         | Additional description: Acute kidney injury                         |                |  |
| subjects affected / exposed                 | 1 / 75 (1.33%)  | 0 / 74 (0.00%) |  |
| occurrences (all)                           | 1   | 0              |  |
| Cystitis noninfective                       | Additional description: Cystitis noninfective                       |                |  |
| subjects affected / exposed                 | 0 / 75 (0.00%)  | 1 / 74 (1.35%) |  |
| occurrences (all)                           | 0   | 1              |  |
| Dysuria                                     | Additional description: Dysuria                                     |                |  |

|   |   |                  |  |
|---|---|------------------|--|
| subjects affected / exposed                     | 1 / 75 (1.33%)                                    | 1 / 74 (1.35%)   |  |
| occurrences (all)                               | 1   | 1                |  |
| Haematuria                                      | Additional description: Haematuria                |                  |  |
| subjects affected / exposed                     | 1 / 75 (1.33%)                                    | 0 / 74 (0.00%)   |  |
| occurrences (all)                               | 1   | 0                |  |
| Pollakiuria                                     | Additional description: Pollakiuria               |                  |  |
| subjects affected / exposed                     | 2 / 75 (2.67%)                                    | 2 / 74 (2.70%)   |  |
| occurrences (all)                               | 2   | 2                |  |
| Renal colic                                     | Additional description: Renal colic               |                  |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)                                    | 1 / 74 (1.35%)   |  |
| occurrences (all)                               | 0   | 1                |  |
| Renal failure                                   | Additional description: Renal failure             |                  |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)                                    | 2 / 74 (2.70%)   |  |
| occurrences (all)                               | 0   | 4                |  |
| Renal pain                                      | Additional description: Renal pain                |                  |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)                                    | 1 / 74 (1.35%)   |  |
| occurrences (all)                               | 0   | 1                |  |
| Urinary retention                               | Additional description: Urinary retention         |                  |  |
| subjects affected / exposed                     | 1 / 75 (1.33%)                                    | 1 / 74 (1.35%)   |  |
| occurrences (all)                               | 1   | 1                |  |
| Urinary tract obstruction                       | Additional description: Urinary tract obstruction |                  |  |
| subjects affected / exposed                     | 0 / 75 (0.00%)                                    | 1 / 74 (1.35%)   |  |
| occurrences (all)                               | 0   | 1                |  |
| Musculoskeletal and connective tissue disorders |   |                  |  |
| Arthralgia                                      | Additional description: Arthralgia                |                  |  |
| subjects affected / exposed                     | 3 / 75 (4.00%)                                    | 11 / 74 (14.86%) |  |
| occurrences (all)                               | 4   | 34               |  |
| Back pain                                       | Additional description: Back pain                 |                  |  |
| subjects affected / exposed                     | 4 / 75 (5.33%)                                    | 9 / 74 (12.16%)  |  |
| occurrences (all)                               | 8   | 21               |  |
| Bone pain                                       | Additional description: Bone pain                 |                  |  |
| subjects affected / exposed                     | 1 / 75 (1.33%)                                    | 1 / 74 (1.35%)   |  |
| occurrences (all)                               | 2   | 3                |  |
| Fistula   | Additional description: Fistula                   |                  |  |

|                             |  |                  |  |
|-----------------------------|--|------------------|--|
| subjects affected / exposed | 1 / 75 (1.33%)                                     | 0 / 74 (0.00%)   |  |
| occurrences (all)           | 2  | 0                |  |
| -----                       |  |                  |  |
| Groin pain                  | Additional description: Groin pain                 |                  |  |
| subjects affected / exposed | 0 / 75 (0.00%)                                     | 1 / 74 (1.35%)   |  |
| occurrences (all)           | 0  | 1                |  |
| -----                       |  |                  |  |
| Joint swelling              | Additional description: Joint swelling             |                  |  |
| subjects affected / exposed | 0 / 75 (0.00%)                                     | 1 / 74 (1.35%)   |  |
| occurrences (all)           | 0  | 1                |  |
| -----                       |  |                  |  |
| Muscle spasms               | Additional description: Muscle spasms              |                  |  |
| subjects affected / exposed | 0 / 75 (0.00%)                                     | 3 / 74 (4.05%)   |  |
| occurrences (all)           | 0  | 9                |  |
| -----                       |  |                  |  |
| Muscular weakness           | Additional description: Muscular weakness          |                  |  |
| subjects affected / exposed | 0 / 75 (0.00%)                                     | 2 / 74 (2.70%)   |  |
| occurrences (all)           | 0  | 3                |  |
| -----                       |  |                  |  |
| Musculoskeletal chest pain  | Additional description: Musculoskeletal chest pain |                  |  |
| subjects affected / exposed | 0 / 75 (0.00%)                                     | 2 / 74 (2.70%)   |  |
| occurrences (all)           | 0  | 6                |  |
| -----                       |  |                  |  |
| Musculoskeletal pain        | Additional description: Musculoskeletal pain       |                  |  |
| subjects affected / exposed | 1 / 75 (1.33%)                                     | 0 / 74 (0.00%)   |  |
| occurrences (all)           | 5  | 0                |  |
| -----                       |  |                  |  |
| Myalgia                     | Additional description: Myalgia                    |                  |  |
| subjects affected / exposed | 3 / 75 (4.00%)                                     | 11 / 74 (14.86%) |  |
| occurrences (all)           | 6  | 24               |  |
| -----                       |  |                  |  |
| Neck pain                   | Additional description: Neck pain                  |                  |  |
| subjects affected / exposed | 1 / 75 (1.33%)                                     | 5 / 74 (6.76%)   |  |
| occurrences (all)           | 1  | 14               |  |
| -----                       |  |                  |  |
| Osteoarthritis              | Additional description: Osteoarthritis             |                  |  |
| subjects affected / exposed | 2 / 75 (2.67%)                                     | 1 / 74 (1.35%)   |  |
| occurrences (all)           | 4  | 2                |  |
| -----                       |  |                  |  |
| Pain in jaw                 | Additional description: Pain in jaw                |                  |  |
| subjects affected / exposed | 0 / 75 (0.00%)                                     | 2 / 74 (2.70%)   |  |
| occurrences (all)           | 0  | 2                |  |
| -----                       |  |                  |  |
| Pain in extremity           | Additional description: Pain in extremity          |                  |  |
| subjects affected / exposed | 4 / 75 (5.33%)                                     | 3 / 74 (4.05%)   |  |
| occurrences (all)           | 11   | 6                |  |
| -----                       |  |                  |  |
| Rhabdomyolysis              | Additional description: Rhabdomyolysis             |                  |  |

|                             |  |                |  |
|-----------------------------|--|----------------|--|
| subjects affected / exposed | 0 / 75 (0.00%)                                   | 1 / 74 (1.35%) |  |
| occurrences (all)           | 0  | 1              |  |
| Spinal pain                 | Additional description: Spinal pain              |                |  |
| subjects affected / exposed | 1 / 75 (1.33%)                                   | 0 / 74 (0.00%) |  |
| occurrences (all)           | 1  | 0              |  |
| Infections and infestations |  |                |  |
| Bronchitis                  | Additional description: Bronchitis               |                |  |
| subjects affected / exposed | 2 / 75 (2.67%)                                   | 4 / 74 (5.41%) |  |
| occurrences (all)           | 2  | 6              |  |
| Conjunctivitis              | Additional description: Conjunctivitis           |                |  |
| subjects affected / exposed | 2 / 75 (2.67%)                                   | 0 / 74 (0.00%) |  |
| occurrences (all)           | 2  | 0              |  |
| Cystitis                    | Additional description: Cystitis                 |                |  |
| subjects affected / exposed | 1 / 75 (1.33%)                                   | 2 / 74 (2.70%) |  |
| occurrences (all)           | 1  | 2              |  |
| Device related infection    | Additional description: Device related infection |                |  |
| subjects affected / exposed | 0 / 75 (0.00%)                                   | 2 / 74 (2.70%) |  |
| occurrences (all)           | 0  | 2              |  |
| Ear infection               | Additional description: Ear infection            |                |  |
| subjects affected / exposed | 0 / 75 (0.00%)                                   | 1 / 74 (1.35%) |  |
| occurrences (all)           | 0  | 1              |  |
| Enterocolitis infectious    | Additional description: Enterocolitis infectious |                |  |
| subjects affected / exposed | 0 / 75 (0.00%)                                   | 1 / 74 (1.35%) |  |
| occurrences (all)           | 0  | 1              |  |
| Folliculitis                | Additional description: Folliculitis             |                |  |
| subjects affected / exposed | 0 / 75 (0.00%)                                   | 3 / 74 (4.05%) |  |
| occurrences (all)           | 0  | 5              |  |
| Fungal infection            | Additional description: Fungal infection         |                |  |
| subjects affected / exposed | 0 / 75 (0.00%)                                   | 1 / 74 (1.35%) |  |
| occurrences (all)           | 0  | 2              |  |
| Gingivitis                  | Additional description: Gingivitis               |                |  |
| subjects affected / exposed | 1 / 75 (1.33%)                                   | 1 / 74 (1.35%) |  |
| occurrences (all)           | 1  | 11             |  |
| Haematoma infection         | Additional description: Haematoma infection      |                |  |
| subjects affected / exposed | 0 / 75 (0.00%)                                   | 1 / 74 (1.35%) |  |
| occurrences (all)           | 0  | 1              |  |

|                             |  |                |
|-----------------------------|--|----------------|
| Herpes virus infection      | Additional description: Herpes virus infection |                |
| subjects affected / exposed | 0 / 75 (0.00%)                                 | 2 / 74 (2.70%) |
| occurrences (all)           | 0  | 3              |
| Herpes zoster               | Additional description: Herpes zoster          |                |
| subjects affected / exposed | 0 / 75 (0.00%)                                 | 1 / 74 (1.35%) |
| occurrences (all)           | 0  | 1              |
| Infection                   | Additional description: Infection              |                |
| subjects affected / exposed | 2 / 75 (2.67%)                                 | 0 / 74 (0.00%) |
| occurrences (all)           | 2  | 0              |
| Localised infection         | Additional description: Localised infection    |                |
| subjects affected / exposed | 0 / 75 (0.00%)                                 | 2 / 74 (2.70%) |
| occurrences (all)           | 0  | 9              |
| Nasopharyngitis             | Additional description: Nasopharyngitis        |                |
| subjects affected / exposed | 2 / 75 (2.67%)                                 | 4 / 74 (5.41%) |
| occurrences (all)           | 2  | 5              |
| Onychomycosis               | Additional description: Onychomycosis          |                |
| subjects affected / exposed | 0 / 75 (0.00%)                                 | 1 / 74 (1.35%) |
| occurrences (all)           | 0  | 1              |
| Oral herpes                 | Additional description: Oral herpes            |                |
| subjects affected / exposed | 0 / 75 (0.00%)                                 | 1 / 74 (1.35%) |
| occurrences (all)           | 0  | 2              |
| Oral fungal infection       | Additional description: Oral fungal infection  |                |
| subjects affected / exposed | 1 / 75 (1.33%)                                 | 1 / 74 (1.35%) |
| occurrences (all)           | 1  | 1              |
| Otitis externa              | Additional description: Otitis externa         |                |
| subjects affected / exposed | 1 / 75 (1.33%)                                 | 0 / 74 (0.00%) |
| occurrences (all)           | 1  | 0              |
| Pharyngitis                 | Additional description: Pharyngitis            |                |
| subjects affected / exposed | 1 / 75 (1.33%)                                 | 1 / 74 (1.35%) |
| occurrences (all)           | 1  | 1              |
| Pyelonephritis              | Additional description: Pyelonephritis         |                |
| subjects affected / exposed | 2 / 75 (2.67%)                                 | 0 / 74 (0.00%) |
| occurrences (all)           | 2  | 0              |
| Rhinitis                    | Additional description: Rhinitis               |                |
| subjects affected / exposed | 0 / 75 (0.00%)                                 | 3 / 74 (4.05%) |
| occurrences (all)           | 0  | 8              |

|   |   |                        |
|---|---|------------------------|
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Sinusitis               |                        |
|   | 1 / 75 (1.33%)<br>1                             | 0 / 74 (0.00%)<br>0    |
| Skin infection<br>subjects affected / exposed<br>occurrences (all)          | Additional description: Skin infection          |                        |
|   | 1 / 75 (1.33%)<br>1                             | 0 / 74 (0.00%)<br>0    |
| Tooth abscess<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Tooth abscess           |                        |
|   | 0 / 75 (0.00%)<br>0                             | 2 / 74 (2.70%)<br>2    |
| Tracheitis<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Tracheitis              |                        |
|   | 0 / 75 (0.00%)<br>0                             | 4 / 74 (5.41%)<br>4    |
| Tooth infection<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Tooth infection         |                        |
|   | 1 / 75 (1.33%)<br>1                             | 1 / 74 (1.35%)<br>2    |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | Additional description: Urinary tract infection |                        |
|   | 3 / 75 (4.00%)<br>3                             | 6 / 74 (8.11%)<br>9    |
| Viral infection<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Viral infection         |                        |
|   | 0 / 75 (0.00%)<br>0                             | 1 / 74 (1.35%)<br>2    |
| Viral pharyngitis<br>subjects affected / exposed<br>occurrences (all)       | Additional description: Viral pharyngitis       |                        |
|   | 1 / 75 (1.33%)<br>1                             | 0 / 74 (0.00%)<br>0    |
| Viral rhinitis<br>subjects affected / exposed<br>occurrences (all)          | Additional description: Viral rhinitis          |                        |
|   | 0 / 75 (0.00%)<br>0                             | 1 / 74 (1.35%)<br>1    |
| Metabolism and nutrition disorders  |   |                        |
| Cell death<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Cell death              |                        |
|   | 0 / 75 (0.00%)<br>0                             | 6 / 74 (8.11%)<br>7    |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)      | Additional description: Decreased appetite      |                        |
|   | 15 / 75 (20.00%)<br>34                          | 22 / 74 (29.73%)<br>60 |
| Dehydration   | Additional description: Dehydration             |                        |



|                             |   |                |  |
|-----------------------------|---|----------------|--|
| subjects affected / exposed | 0 / 75 (0.00%)                                | 1 / 74 (1.35%) |  |
| occurrences (all)           | 0   | 1              |  |
| Hypercalcaemia              | Additional description: Hypercalcaemia        |                |  |
| subjects affected / exposed | 1 / 75 (1.33%)                                | 1 / 74 (1.35%) |  |
| occurrences (all)           | 1   | 12             |  |
| Hyperkalaemia               | Additional description: Hyperkalaemia         |                |  |
| subjects affected / exposed | 0 / 75 (0.00%)                                | 2 / 74 (2.70%) |  |
| occurrences (all)           | 0   | 6              |  |
| Hyperglycaemia              | Additional description: Hyperglycaemia        |                |  |
| subjects affected / exposed | 0 / 75 (0.00%)                                | 2 / 74 (2.70%) |  |
| occurrences (all)           | 0   | 3              |  |
| Hypoalbuminaemia            | Additional description: Hypoalbuminaemia      |                |  |
| subjects affected / exposed | 0 / 75 (0.00%)                                | 5 / 74 (6.76%) |  |
| occurrences (all)           | 0   | 12             |  |
| Hypocalcaemia               | Additional description: Hypocalcaemia         |                |  |
| subjects affected / exposed | 0 / 75 (0.00%)                                | 2 / 74 (2.70%) |  |
| occurrences (all)           | 0   | 3              |  |
| Hypoglycaemia               | Additional description: Hypoglycaemia         |                |  |
| subjects affected / exposed | 0 / 75 (0.00%)                                | 1 / 74 (1.35%) |  |
| occurrences (all)           | 0   | 1              |  |
| Hypokalaemia                | Additional description: Hypokalaemia          |                |  |
| subjects affected / exposed | 0 / 75 (0.00%)                                | 3 / 74 (4.05%) |  |
| occurrences (all)           | 0   | 7              |  |
| Malnutrition                | Additional description: Malnutrition          |                |  |
| subjects affected / exposed | 0 / 75 (0.00%)                                | 1 / 74 (1.35%) |  |
| occurrences (all)           | 0   | 1              |  |
| Tumour lysis syndrome       | Additional description: Tumour lysis syndrome |                |  |
| subjects affected / exposed | 0 / 75 (0.00%)                                | 1 / 74 (1.35%) |  |
| occurrences (all)           | 0   | 1              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment   |
|---------------|---|
| 11 April 2017 | The information notice for the patients was modified following the update of the investigator's brochure. |
| 20 April 2018 | The information notice for the patients was modified following the update of the investigator's brochure. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported