



## Clinical trial results:

### A RANDOMIZED PHASE 2 TRIAL OF AXITINIB AND TRC105 VERSUS AXITINIB ALONE (INCLUDING A LEAD-IN PHASE 1B DOSE-ESCALATION PORTION) IN PATIENTS WITH ADVANCED OR METASTATIC RENAL CELL CARCINOMA

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-003436-13 |
| Trial protocol           | HU GB PL CZ    |
| Global end of trial date | 12 June 2019   |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 02 June 2021 |
| First version publication date | 02 June 2021 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 105RC101 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01806064 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                            |
|------------------------------|--------------------------------------------------------------------------------------------|
| Sponsor organisation name    | TRACON Pharmaceuticals, Inc.                                                               |
| Sponsor organisation address | 4350 La Jolla Village Drive, Suite 800, San Diego, United States, 92010                    |
| Public contact               | Study Manager, TRACON Pharmaceuticals Inc., +1 8585500780, clinicaltrials@traconpharma.com |
| Scientific contact           | Study Manager, TRACON Pharmaceuticals Inc., +1 8585500780, clinicaltrials@traconpharma.com |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 12 June 2019     |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 21 December 2018 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 12 June 2019     |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

Phase 1b: To evaluate safety and tolerability and determine a recommended phase 2 dose for TRC105 when added to standard dose axitinib in patients with renal cell carcinoma.

Phase 2: To estimate the PFS of patients with advanced or metastatic RCC by RECIST 1.1 criteria in patients treated with axitinib and TRC105 compared to those treated with axitinib alone, following failure of one prior VEGF inhibitor

Protection of trial subjects:

Safety parameters were reviewed by a chartered Safety Review Team that reviewed data for all TRC105 studies quarterly and a chartered Data Monitoring Committee (DMC) that periodically reviewed accumulating safety and efficacy data from this study. An interim analysis for futility was conducted by the DMC when 55 events occurred. At the interim analysis, the conditional power based on the observed hazard ratio was estimated. If the conditional power was less than 25%, the DMC could recommend the sponsor that the study be terminated for futility. This interim analysis did not consider the possibility of early termination on the basis of superior efficacy.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 18 December 2015 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 1  |
| Country: Number of subjects enrolled | Czechia: 13        |
| Country: Number of subjects enrolled | Hungary: 21        |
| Country: Number of subjects enrolled | United States: 138 |
| Worldwide total number of subjects   | 173                |
| EEA total number of subjects         | 34                 |

Notes:

### Subjects enrolled per age group

|                                        |   |
|----------------------------------------|---|
| In utero                               | 0 |
| Preterm newborn - gestational age < 37 | 0 |

|                                          |    |
|------------------------------------------|----|
| wk                                       |    |
| 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)                     | 93 |
| From 65 to 84 years                      | 80 |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details:

23 patients enrolled in phase 1b portion. 150 patients randomized in the phase 2 portion.

### Pre-assignment

Screening details:

Patients with advanced or metastatic renal cell carcinoma.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Trial (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> | P2 Arm A: 5 mg Axitinib BID |
|------------------|-----------------------------|

Arm description:

Phase 2 Arm A: 5 mg Axitinib twice daily

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

Dosage and administration details:

1mg and 5mg tablets

|                  |                                                    |
|------------------|----------------------------------------------------|
| <b>Arm title</b> | P2 Arm B: 10 mg/kg TRC105 Wkly + 5 mg Axitinib BID |
|------------------|----------------------------------------------------|

Arm description:

Phase 2 Arm B: 10 mg/kg TRC105 weekly + 5 mg Axitinib twice daily

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

Dosage and administration details:

5mg tablets twice daily

|                                        |                                       |
|----------------------------------------|---------------------------------------|
| Investigational medicinal product name | TRC 105                               |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

10mg/kg Weekly

|                  |                                              |
|------------------|----------------------------------------------|
| <b>Arm title</b> | P1b: 8 mg/kg TRC105 Wkly + 5 mg Axitinib BID |
|------------------|----------------------------------------------|

Arm description:

Phase 1b Dose Level 1: 8 mg/kg TRC105 weekly in combination with 5 mg Axitinib twice daily

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

|                                                                                                                                                                      |                                                              |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| Investigational medicinal product name                                                                                                                               | Axitinib                                                     |
| Investigational medicinal product code                                                                                                                               |                                                              |
| Other name                                                                                                                                                           |                                                              |
| Pharmaceutical forms                                                                                                                                                 | Tablet                                                       |
| Routes of administration                                                                                                                                             | Oral use                                                     |
| Dosage and administration details:                                                                                                                                   |                                                              |
| 5mg tablets twice daily                                                                                                                                              |                                                              |
| Investigational medicinal product name                                                                                                                               | TRC 105                                                      |
| Investigational medicinal product code                                                                                                                               |                                                              |
| Other name                                                                                                                                                           |                                                              |
| Pharmaceutical forms                                                                                                                                                 | Concentrate for solution for infusion                        |
| Routes of administration                                                                                                                                             | Intravenous use                                              |
| Dosage and administration details:                                                                                                                                   |                                                              |
| 8mg/kg Weekly                                                                                                                                                        |                                                              |
| <b>Arm title</b>                                                                                                                                                     | P1b: 10 mg/kg TRC105 Wkly + 5 mg Axitinib BID                |
| Arm description:                                                                                                                                                     |                                                              |
| Phase 1b Dose Level 2: 10 mg/kg TRC105 weekly in combination with 5 mg Axitinib twice daily                                                                          |                                                              |
| Arm type                                                                                                                                                             | Experimental                                                 |
| Investigational medicinal product name                                                                                                                               | Axitinib                                                     |
| Investigational medicinal product code                                                                                                                               |                                                              |
| Other name                                                                                                                                                           |                                                              |
| Pharmaceutical forms                                                                                                                                                 | Tablet                                                       |
| Routes of administration                                                                                                                                             | Oral use                                                     |
| Dosage and administration details:                                                                                                                                   |                                                              |
| 5mg tablets twice daily                                                                                                                                              |                                                              |
| Investigational medicinal product name                                                                                                                               | TRC 105                                                      |
| Investigational medicinal product code                                                                                                                               |                                                              |
| Other name                                                                                                                                                           |                                                              |
| Pharmaceutical forms                                                                                                                                                 | Concentrate for solution for infusion                        |
| Routes of administration                                                                                                                                             | Intravenous use                                              |
| Dosage and administration details:                                                                                                                                   |                                                              |
| 10mg/kg Weekly                                                                                                                                                       |                                                              |
| <b>Arm title</b>                                                                                                                                                     | P1b: 10 mg/kg Wkly/15 mg/kg q2wks TRC105 + 5 mg Axitinib BID |
| Arm description:                                                                                                                                                     |                                                              |
| Phase 1b Dose Level 3: 10 mg/kg TRC105 weekly during cycle 1 then 15 mg/kg TRC105 every two weeks beginning in cycle 2 in combination with 5 mg Axitinib twice daily |                                                              |
| Arm type                                                                                                                                                             | Experimental                                                 |
| Investigational medicinal product name                                                                                                                               | Axitinib                                                     |
| Investigational medicinal product code                                                                                                                               |                                                              |
| Other name                                                                                                                                                           |                                                              |
| Pharmaceutical forms                                                                                                                                                 | Tablet                                                       |
| Routes of administration                                                                                                                                             | Oral use                                                     |
| Dosage and administration details:                                                                                                                                   |                                                              |
| 5mg tablets twice daily                                                                                                                                              |                                                              |
| Investigational medicinal product name                                                                                                                               | TRC 105                                                      |
| Investigational medicinal product code                                                                                                                               |                                                              |
| Other name                                                                                                                                                           |                                                              |
| Pharmaceutical forms                                                                                                                                                 | Concentrate for solution for infusion                        |
| Routes of administration                                                                                                                                             | Intravenous use                                              |
| Dosage and administration details:                                                                                                                                   |                                                              |
| 10 mg/kg TRC105 weekly during cycle 1 then 15 mg/kg TRC105 every two weeks beginning in cycle 2                                                                      |                                                              |

| Number of subjects in period 1 | P2 Arm A: 5 mg<br>Axitinib BID | P2 Arm B: 10 mg/kg<br>TRC105 Wkly + 5<br>mg Axitinib BID | P1b: 8 mg/kg<br>TRC105 Wkly + 5<br>mg Axitinib BID |
|--------------------------------|--------------------------------|----------------------------------------------------------|----------------------------------------------------|
|                                |                                |                                                          |                                                    |
| Started                        | 75                             | 75                                                       | 3                                                  |
| Completed                      | 74                             | 73                                                       | 3                                                  |
| Not completed                  | 1                              | 2                                                        | 0                                                  |
| Randomized not enrolled        | 1                              | 2                                                        | -                                                  |

| Number of subjects in period 1 | P1b: 10 mg/kg<br>TRC105 Wkly + 5<br>mg Axitinib BID | P1b: 10 mg/kg<br>Wkly/15 mg/kg<br>q2wks TRC105 + 5<br>mg Axitinib BID |
|--------------------------------|-----------------------------------------------------|-----------------------------------------------------------------------|
|                                |                                                     |                                                                       |
| Started                        | 15                                                  | 5                                                                     |
| Completed                      | 15                                                  | 5                                                                     |
| Not completed                  | 0                                                   | 0                                                                     |
| Randomized not enrolled        | -                                                   | -                                                                     |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                      |                                                              |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| Reporting group title                                                                                                                                                | P2 Arm A: 5 mg Axitinib BID                                  |
| Reporting group description:                                                                                                                                         |                                                              |
| Phase 2 Arm A: 5 mg Axitinib twice daily                                                                                                                             |                                                              |
| Reporting group title                                                                                                                                                | P2 Arm B: 10 mg/kg TRC105 Wkly + 5 mg Axitinib BID           |
| Reporting group description:                                                                                                                                         |                                                              |
| Phase 2 Arm B: 10 mg/kg TRC105 weekly + 5 mg Axitinib twice daily                                                                                                    |                                                              |
| Reporting group title                                                                                                                                                | P1b: 8 mg/kg TRC105 Wkly + 5 mg Axitinib BID                 |
| Reporting group description:                                                                                                                                         |                                                              |
| Phase 1b Dose Level 1: 8 mg/kg TRC105 weekly in combination with 5 mg Axitinib twice daily                                                                           |                                                              |
| Reporting group title                                                                                                                                                | P1b: 10 mg/kg TRC105 Wkly + 5 mg Axitinib BID                |
| Reporting group description:                                                                                                                                         |                                                              |
| Phase 1b Dose Level 2: 10 mg/kg TRC105 weekly in combination with 5 mg Axitinib twice daily                                                                          |                                                              |
| Reporting group title                                                                                                                                                | P1b: 10 mg/kg Wkly/15 mg/kg q2wks TRC105 + 5 mg Axitinib BID |
| Reporting group description:                                                                                                                                         |                                                              |
| Phase 1b Dose Level 3: 10 mg/kg TRC105 weekly during cycle 1 then 15 mg/kg TRC105 every two weeks beginning in cycle 2 in combination with 5 mg Axitinib twice daily |                                                              |

| Reporting group values                                                       | P2 Arm A: 5 mg Axitinib BID | P2 Arm B: 10 mg/kg TRC105 Wkly + 5 mg Axitinib BID | P1b: 8 mg/kg TRC105 Wkly + 5 mg Axitinib BID |
|------------------------------------------------------------------------------|-----------------------------|----------------------------------------------------|----------------------------------------------|
| Number of subjects                                                           | 75                          | 75                                                 | 3                                            |
| Age categorical                                                              |                             |                                                    |                                              |
| All patients who received at least a portion of a dose of TRC105 or axitinib |                             |                                                    |                                              |
| Units: Subjects                                                              |                             |                                                    |                                              |
| Adults (18-64 years)                                                         | 35                          | 43                                                 | 0                                            |
| From 65-84 years                                                             | 40                          | 32                                                 | 3                                            |
| Gender categorical                                                           |                             |                                                    |                                              |
| All patients who received at least a portion of a dose of TRC105 or axitinib |                             |                                                    |                                              |
| Units: Subjects                                                              |                             |                                                    |                                              |
| Female                                                                       | 18                          | 26                                                 | 0                                            |
| Male                                                                         | 57                          | 49                                                 | 3                                            |
| Race/Ethnicity                                                               |                             |                                                    |                                              |
| All patients who received at least a portion of a dose of TRC105 or axitinib |                             |                                                    |                                              |
| Units: Subjects                                                              |                             |                                                    |                                              |
| Caucasian                                                                    | 70                          | 71                                                 | 3                                            |
| Hispanic or Latino                                                           | 5                           | 1                                                  | 0                                            |
| American Indian or Alaska Native                                             | 0                           | 2                                                  | 0                                            |
| Native Hawaiian or other Pacific Islander                                    | 0                           | 1                                                  | 0                                            |
| Region of Enrollment                                                         |                             |                                                    |                                              |
| All patients who received at least a portion of a dose of TRC105 or axitinib |                             |                                                    |                                              |
| Units: Subjects                                                              |                             |                                                    |                                              |
| Hungary                                                                      | 11                          | 10                                                 | 0                                            |
| United States                                                                | 56                          | 59                                                 | 3                                            |
| Czechia                                                                      | 8                           | 5                                                  | 0                                            |
| United Kingdom                                                               | 0                           | 1                                                  | 0                                            |

| <b>Reporting group values</b>                                                | P1b: 10 mg/kg TRC105 Wkly + 5 mg Axitinib BID | P1b: 10 mg/kg Wkly/15 mg/kg q2wks TRC105 + 5 mg Axitinib BID | Total |
|------------------------------------------------------------------------------|-----------------------------------------------|--------------------------------------------------------------|-------|
| Number of subjects                                                           | 15                                            | 5                                                            | 173   |
| Age categorical                                                              |                                               |                                                              |       |
| All patients who received at least a portion of a dose of TRC105 or axitinib |                                               |                                                              |       |
| Units: Subjects                                                              |                                               |                                                              |       |
| Adults (18-64 years)                                                         | 13                                            | 2                                                            | 93    |
| From 65-84 years                                                             | 2                                             | 3                                                            | 80    |
| Gender categorical                                                           |                                               |                                                              |       |
| All patients who received at least a portion of a dose of TRC105 or axitinib |                                               |                                                              |       |
| Units: Subjects                                                              |                                               |                                                              |       |
| Female                                                                       | 2                                             | 2                                                            | 48    |
| Male                                                                         | 13                                            | 3                                                            | 125   |
| Race/Ethnicity                                                               |                                               |                                                              |       |
| All patients who received at least a portion of a dose of TRC105 or axitinib |                                               |                                                              |       |
| Units: Subjects                                                              |                                               |                                                              |       |
| Caucasian                                                                    | 12                                            | 5                                                            | 161   |
| Hispanic or Latino                                                           | 3                                             | 0                                                            | 9     |
| American Indian or Alaska Native                                             | 0                                             | 0                                                            | 2     |
| Native Hawaiian or other Pacific Islander                                    | 0                                             | 0                                                            | 1     |
| Region of Enrollment                                                         |                                               |                                                              |       |
| All patients who received at least a portion of a dose of TRC105 or axitinib |                                               |                                                              |       |
| Units: Subjects                                                              |                                               |                                                              |       |
| Hungary                                                                      | 0                                             | 0                                                            | 21    |
| United States                                                                | 15                                            | 5                                                            | 138   |
| Czechia                                                                      | 0                                             | 0                                                            | 13    |
| United Kingdom                                                               | 0                                             | 0                                                            | 1     |

## End points

### End points reporting groups

|                                                                                                                                                                                                      |                                                              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| Reporting group title                                                                                                                                                                                | P2 Arm A: 5 mg Axitinib BID                                  |
| Reporting group description:<br>Phase 2 Arm A: 5 mg Axitinib twice daily                                                                                                                             |                                                              |
| Reporting group title                                                                                                                                                                                | P2 Arm B: 10 mg/kg TRC105 Wkly + 5 mg Axitinib BID           |
| Reporting group description:<br>Phase 2 Arm B: 10 mg/kg TRC105 weekly + 5 mg Axitinib twice daily                                                                                                    |                                                              |
| Reporting group title                                                                                                                                                                                | P1b: 8 mg/kg TRC105 Wkly + 5 mg Axitinib BID                 |
| Reporting group description:<br>Phase 1b Dose Level 1: 8 mg/kg TRC105 weekly in combination with 5 mg Axitinib twice daily                                                                           |                                                              |
| Reporting group title                                                                                                                                                                                | P1b: 10 mg/kg TRC105 Wkly + 5 mg Axitinib BID                |
| Reporting group description:<br>Phase 1b Dose Level 2: 10 mg/kg TRC105 weekly in combination with 5 mg Axitinib twice daily                                                                          |                                                              |
| Reporting group title                                                                                                                                                                                | P1b: 10 mg/kg Wkly/15 mg/kg q2wks TRC105 + 5 mg Axitinib BID |
| Reporting group description:<br>Phase 1b Dose Level 3: 10 mg/kg TRC105 weekly during cycle 1 then 15 mg/kg TRC105 every two weeks beginning in cycle 2 in combination with 5 mg Axitinib twice daily |                                                              |

### Primary: Phase 1b: Number of Patients with DLT

|                                                                                                                                                                                                                                                                                                                     |                                                         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                     | Phase 1b: Number of Patients with DLT <sup>[1][2]</sup> |
| End point description:<br>Phase 1b: For dose limiting toxicity (DLT) evaluation, severity (grade) was classified according to common terminology criteria for adverse events version 4.0 (CTCAE v4.0).<br><br>Patients who discontinued the study prior to completing the DLT evaluation period were not evaluable. |                                                         |
| End point type                                                                                                                                                                                                                                                                                                      | Primary                                                 |
| End point timeframe:<br>12 Months                                                                                                                                                                                                                                                                                   |                                                         |

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: In Phase 1b there were no dose limiting toxicities.

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

Justification: For Phase 2 the number of patients with DLT was not measured.

| End point values            | P1b: 8 mg/kg TRC105 Wkly + 5 mg Axitinib BID | P1b: 10 mg/kg TRC105 Wkly + 5 mg Axitinib BID | P1b: 10 mg/kg Wkly/15 mg/kg q2wks TRC105 + 5 mg Axitinib BID |  |
|-----------------------------|----------------------------------------------|-----------------------------------------------|--------------------------------------------------------------|--|
| Subject group type          | Reporting group                              | Reporting group                               | Reporting group                                              |  |
| Number of subjects analysed | 3                                            | 15                                            | 5                                                            |  |
| Units: Participants         | 0                                            | 0                                             | 0                                                            |  |

### Statistical analyses

**Primary: Phase 2: Progression free survival (PFS) of patients with RCC**

|                 |                                                                              |
|-----------------|------------------------------------------------------------------------------|
| End point title | Phase 2: Progression free survival (PFS) of patients with RCC <sup>[3]</sup> |
|-----------------|------------------------------------------------------------------------------|

End point description:

Median progression free survival (PFS) of patients with advanced or metastatic RCC by RECIST 1.1. Progression is defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1), as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions.

For Phase 2 all randomized patients were included in the efficacy population.

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

End point timeframe:

15 Months

Notes:

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

Justification: PFS was not measured in Phase 1b.

| End point values                 | P2 Arm A: 5 mg Axitinib BID | P2 Arm B: 10 mg/kg TRC105 Wkly + 5 mg Axitinib BID |  |  |
|----------------------------------|-----------------------------|----------------------------------------------------|--|--|
| Subject group type               | Reporting group             | Reporting group                                    |  |  |
| Number of subjects analysed      | 75                          | 75                                                 |  |  |
| Units: Months                    |                             |                                                    |  |  |
| median (confidence interval 95%) | 11.4 (5.8 to 13)            | 6.7 (5.6 to 13.1)                                  |  |  |

**Statistical analyses**

|                            |             |
|----------------------------|-------------|
| Statistical analysis title | Comparative |
|----------------------------|-------------|

Statistical analysis description:

PFS comparison between Arm A and Arm B.

|                                         |                                                                                  |
|-----------------------------------------|----------------------------------------------------------------------------------|
| Comparison groups                       | P2 Arm A: 5 mg Axitinib BID v P2 Arm B: 10 mg/kg TRC105 Wkly + 5 mg Axitinib BID |
| Number of subjects included in analysis | 150                                                                              |
| Analysis specification                  | Pre-specified                                                                    |
| Analysis type                           | superiority                                                                      |
| P-value                                 | ≤ 0.1                                                                            |
| Method                                  | Logrank                                                                          |

**Secondary: Phase 1b & 2: Response Rate of patients with RCC**

|                 |                                                  |
|-----------------|--------------------------------------------------|
| End point title | Phase 1b & 2: Response Rate of patients with RCC |
|-----------------|--------------------------------------------------|

End point description:

Number of patients with partial response (PR) or complete response (CR) by RECIST 1.1 criteria. Per Response Evaluation Criteria in Solid Tumors Criteria RECIST v1.1 for target lesions and assessed by MRI: Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), ≥30% decrease in the sum of the longest diameter of target lesions; Overall Response (OR) = CR + PR. For Phase 1b patients with screening and at least 1 on study scan were included in the efficacy population. For Phase 2 all randomized patients were included in the efficacy population. Patients without a baseline scan and at least 1 on study scan were excluded from analysis.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 15 Months            |           |

| End point values            | P2 Arm A: 5 mg Axitinib BID | P2 Arm B: 10 mg/kg TRC105 Wkly + 5 mg Axitinib BID | P1b: 8 mg/kg TRC105 Wkly + 5 mg Axitinib BID | P1b: 10 mg/kg TRC105 Wkly + 5 mg Axitinib BID |
|-----------------------------|-----------------------------|----------------------------------------------------|----------------------------------------------|-----------------------------------------------|
| Subject group type          | Reporting group             | Reporting group                                    | Reporting group                              | Reporting group                               |
| Number of subjects analysed | 75                          | 75                                                 | 3                                            | 14                                            |
| Units: Participants         | 22                          | 23                                                 | 0                                            | 5                                             |

| End point values            | P1b: 10 mg/kg Wkly/15 mg/kg q2wks TRC105 + 5 mg Axitinib BID |  |  |  |
|-----------------------------|--------------------------------------------------------------|--|--|--|
| Subject group type          | Reporting group                                              |  |  |  |
| Number of subjects analysed | 5                                                            |  |  |  |
| Units: Participants         | 0                                                            |  |  |  |

## Statistical analyses

| Statistical analysis title              | Comparative                                                                                                                                                                                                                                    |
|-----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Statistical analysis description:       |                                                                                                                                                                                                                                                |
| Response rate by RECIST 1.1 criteria.   |                                                                                                                                                                                                                                                |
| Comparison groups                       | P2 Arm A: 5 mg Axitinib BID v P2 Arm B: 10 mg/kg TRC105 Wkly + 5 mg Axitinib BID v P1b: 8 mg/kg TRC105 Wkly + 5 mg Axitinib BID v P1b: 10 mg/kg TRC105 Wkly + 5 mg Axitinib BID v P1b: 10 mg/kg Wkly/15 mg/kg q2wks TRC105 + 5 mg Axitinib BID |
| Number of subjects included in analysis | 172                                                                                                                                                                                                                                            |
| Analysis specification                  | Pre-specified                                                                                                                                                                                                                                  |
| Analysis type                           | other <sup>[4]</sup>                                                                                                                                                                                                                           |
| P-value                                 | ≤ 0.1                                                                                                                                                                                                                                          |
| Method                                  | Chi-squared test                                                                                                                                                                                                                               |

Notes:

[4] - Response rate by RECIST in Phase 1b patients (descriptive) and in Phase 2 patients (superiority).

## Secondary: Phase 2: Overall Response Rate of patients with RCC by Choi

| End point title | Phase 2: Overall Response Rate of patients with RCC by Choi <sup>[5]</sup> |
|-----------------|----------------------------------------------------------------------------|
|-----------------|----------------------------------------------------------------------------|

End point description:

Overall response (OR) rate is the number of patients with partial response (PR) or complete response (CR) by Choi Criteria. Per Choi criteria for target lesions and assessed by MRI: Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), A decrease in size ≥ 10% or a decrease in tumor attenuation (Hounsfield units) ≥ 15% on CT and no new lesions; Overall Response (OR) = CR + PR.

For Phase 2 all randomized patients were included in the efficacy population. Patients without a baseline

scan and at least 1 on study scan were excluded from analysis.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 15 Months            |           |

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: For Phase 1b Overall Response Rate of patients with RCC by Choi was not measured.

|                             |                             |                                                    |  |  |
|-----------------------------|-----------------------------|----------------------------------------------------|--|--|
| <b>End point values</b>     | P2 Arm A: 5 mg Axitinib BID | P2 Arm B: 10 mg/kg TRC105 Wkly + 5 mg Axitinib BID |  |  |
| Subject group type          | Reporting group             | Reporting group                                    |  |  |
| Number of subjects analysed | 75                          | 75                                                 |  |  |
| Units: Participants         | 50                          | 50                                                 |  |  |

## Statistical analyses

|                                           |                                                                                  |
|-------------------------------------------|----------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>         | Comparative                                                                      |
| Statistical analysis description:         |                                                                                  |
| The primary endpoint for efficacy is PFS. |                                                                                  |
| Comparison groups                         | P2 Arm B: 10 mg/kg TRC105 Wkly + 5 mg Axitinib BID v P2 Arm A: 5 mg Axitinib BID |
| Number of subjects included in analysis   | 150                                                                              |
| Analysis specification                    | Pre-specified                                                                    |
| Analysis type                             | superiority                                                                      |
| P-value                                   | ≤ 0.1 [6]                                                                        |
| Method                                    | Chi-square                                                                       |

Notes:

[6] - One-sided test

## Secondary: Phase 1b & 2: Trough concentrations of TRC105 by Dose Level in Phase 1b

|                 |                                                                                        |
|-----------------|----------------------------------------------------------------------------------------|
| End point title | Phase 1b & 2: Trough concentrations of TRC105 by Dose Level in Phase 1b <sup>[7]</sup> |
|-----------------|----------------------------------------------------------------------------------------|

End point description:

Trough Serum TRC105 concentrations at steady state (cycle 2 day 15) were measured using validated ELISA methods.

In Phase 1b patients with a predose sample collected at cycle 2 day 15 were averaged. Patients who missed a dose of TRC105 prior to cycle 2 day 15 were excluded from the analysis. Additional Phase 1b PK analysis beyond steady state concentration at cycle 2 day 15 were not performed. Samples collected in the phase 2 portion of the study were not analyzed.

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

End point timeframe:

2.5 months (cycle 2 day 15)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: The study was terminated due to lack of efficacy and samples collected in the phase 2 portion of the study were not analyzed.

| End point values                     | P1b: 8 mg/kg TRC105 Wkly + 5 mg Axitinib BID | P1b: 10 mg/kg TRC105 Wkly + 5 mg Axitinib BID | P1b: 10 mg/kg Wkly/15 mg/kg q2wks TRC105 + 5 mg Axitinib BID |  |
|--------------------------------------|----------------------------------------------|-----------------------------------------------|--------------------------------------------------------------|--|
| Subject group type                   | Reporting group                              | Reporting group                               | Reporting group                                              |  |
| Number of subjects analysed          | 3                                            | 13                                            | 5                                                            |  |
| Units: ng/mL                         |                                              |                                               |                                                              |  |
| arithmetic mean (standard deviation) | 27650 (± 39103)                              | 140022 (± 45403.1)                            | 54375 (± 23546.5)                                            |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Phase 1b & 2: Number of patients with development of immunogenicity antibodies.

|                 |                                                                                                |
|-----------------|------------------------------------------------------------------------------------------------|
| End point title | Phase 1b & 2: Number of patients with development of immunogenicity antibodies. <sup>[8]</sup> |
|-----------------|------------------------------------------------------------------------------------------------|

End point description:

Anti-product antibody concentration were measured using validated ELISA methods.

Patients must have had a baseline and on study assessment of immunogenicity and their baseline must have been negative. Samples collected in the phase 2 portion of the study were not analyzed.

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

End point timeframe:

12 Months

Notes:

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

Justification: The study was terminated early due to lack of efficacy and samples collected in the phase 2 portion of the study were not analyzed.

| End point values            | P1b: 8 mg/kg TRC105 Wkly + 5 mg Axitinib BID | P1b: 10 mg/kg TRC105 Wkly + 5 mg Axitinib BID | P1b: 10 mg/kg Wkly/15 mg/kg q2wks TRC105 + 5 mg Axitinib BID |  |
|-----------------------------|----------------------------------------------|-----------------------------------------------|--------------------------------------------------------------|--|
| Subject group type          | Reporting group                              | Reporting group                               | Reporting group                                              |  |
| Number of subjects analysed | 3                                            | 5                                             | 5                                                            |  |
| Units: Participants         | 1                                            | 0                                             | 0                                                            |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

2 years, 6 months. Only patients who received at least a portion of a dose of TRC105 and/or Axitinib have been included in the analysis population.

Adverse event reporting additional description:

Any untoward or unfavorable medical occurrence in a participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 4.0    |

### Reporting groups

|                       |                                              |
|-----------------------|----------------------------------------------|
| Reporting group title | P1b: 8 mg/kg TRC105 Wkly + 5 mg Axitinib BID |
|-----------------------|----------------------------------------------|

Reporting group description:

Phase 1b Dose Level 1: 8 mg/kg TRC105 weekly in combination with 5 mg Axitinib twice daily

|                       |                                               |
|-----------------------|-----------------------------------------------|
| Reporting group title | P1b: 10 mg/kg TRC105 Wkly + 5 mg Axitinib BID |
|-----------------------|-----------------------------------------------|

Reporting group description:

Phase 1b Dose Level 2: 10 mg/kg TRC105 weekly in combination with 5 mg Axitinib twice daily

|                       |                                                              |
|-----------------------|--------------------------------------------------------------|
| Reporting group title | P1b: 10 mg/kg Wkly/15 mg/kg q2wks TRC105 + 5 mg Axitinib BID |
|-----------------------|--------------------------------------------------------------|

Reporting group description:

Phase 1b Dose Level 3: 10 mg/kg TRC105 weekly during cycle 1 then 15 mg/kg TRC105 every two weeks beginning in cycle 2 in combination with 5 mg Axitinib twice daily

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | P2 Arm A: 5 mg Axitinib BID |
|-----------------------|-----------------------------|

Reporting group description:

Phase 2 Arm A: 5 mg Axitinib twice daily

|                       |                                                    |
|-----------------------|----------------------------------------------------|
| Reporting group title | P2 Arm B: 10 mg/kg TRC105 Wkly + 5 mg Axitinib BID |
|-----------------------|----------------------------------------------------|

Reporting group description:

Phase 2 Arm B: 10 mg/kg TRC105 weekly + 5 mg Axitinib twice daily

| Serious adverse events                                              | P1b: 8 mg/kg TRC105 Wkly + 5 mg Axitinib BID | P1b: 10 mg/kg TRC105 Wkly + 5 mg Axitinib BID | P1b: 10 mg/kg Wkly/15 mg/kg q2wks TRC105 + 5 mg Axitinib BID |
|---------------------------------------------------------------------|----------------------------------------------|-----------------------------------------------|--------------------------------------------------------------|
| Total subjects affected by serious adverse events                   |                                              |                                               |                                                              |
| subjects affected / exposed                                         | 1 / 3 (33.33%)                               | 4 / 15 (26.67%)                               | 3 / 5 (60.00%)                                               |
| number of deaths (all causes)                                       | 0                                            | 1                                             | 0                                                            |
| number of deaths resulting from adverse events                      |                                              |                                               |                                                              |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                              |                                               |                                                              |
| Bronchial Neoplasm                                                  |                                              |                                               |                                                              |

|                                                      |               |                |               |
|------------------------------------------------------|---------------|----------------|---------------|
| subjects affected / exposed                          | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0         |
| Vascular disorders                                   |               |                |               |
| Deep Vein Thrombosis                                 |               |                |               |
| subjects affected / exposed                          | 0 / 3 (0.00%) | 1 / 15 (6.67%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0         |
| Hypertension                                         |               |                |               |
| subjects affected / exposed                          | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0         |
| General disorders and administration site conditions |               |                |               |
| Chest pain                                           |               |                |               |
| subjects affected / exposed                          | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0         |
| Disease Progression                                  |               |                |               |
| subjects affected / exposed                          | 0 / 3 (0.00%) | 1 / 15 (6.67%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 1          | 0 / 0         |
| Fatigue                                              |               |                |               |
| subjects affected / exposed                          | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0         |
| Multi-organ Failure                                  |               |                |               |
| subjects affected / exposed                          | 0 / 3 (0.00%) | 1 / 15 (6.67%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0          | 0 / 0         |
| Reproductive system and breast disorders             |               |                |               |
| Pelvic Pain                                          |               |                |               |

|                                                 |               |                |               |
|-------------------------------------------------|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Respiratory, thoracic and mediastinal disorders |               |                |               |
| Pulmonary Embolism                              |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Pulmonary Haemorrhage                           |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 15 (6.67%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Dyspnoea                                        |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Epistaxis                                       |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Hypoxia                                         |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Pleural Effusion                                |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Pneumothorax                                    |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Respiratory Failure                             |               |                |               |

|                                                 |                |                |               |
|-------------------------------------------------|----------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Vomiting                                        |                |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Psychiatric disorders                           |                |                |               |
| Confusional State                               |                |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Injury, poisoning and procedural complications  |                |                |               |
| Infusion Related Reaction                       |                |                |               |
| subjects affected / exposed                     | 1 / 3 (33.33%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Femur Fracture                                  |                |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Spinal Fracture                                 |                |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Cardiac disorders                               |                |                |               |
| Acute Heart Failure                             |                |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Myocardial Infarction                           |                |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |

|                                                 |               |                |               |
|-------------------------------------------------|---------------|----------------|---------------|
| Nervous system disorders                        |               |                |               |
| Encephalopathy                                  |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Epilepsy                                        |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Hemiparesis                                     |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Haemorrhage Intracranial                        |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Migraine                                        |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Paraparesis                                     |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Posterior Reversible Encephalopathy Syndrome    |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Seizure                                         |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Headache                                        |                |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| Anaemia                                         |                |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Eye disorders                                   |                |                |                |
| Retinal Vein Occlusion                          |                |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Abdominal Pain                                  |                |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 15 (6.67%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gallbladder Perforation                         |                |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Colitis                                         |                |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diarrhoea                                       |                |                |                |
| subjects affected / exposed                     | 1 / 3 (33.33%) | 0 / 15 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Oesophageal Ulcer Haemorrhage                   |                |                |                |

|                                                 |               |                |               |
|-------------------------------------------------|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Colonic Perforation                             |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Gastrointestinal Perforation                    |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Gastrointestinal Haemorrhage                    |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Lower Gastrointestinal Haemorrhage              |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Pancreatitis                                    |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Pyrexia                                         |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 15 (6.67%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Hepatobiliary disorders                         |               |                |               |
| Liver Injury                                    |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Cholecystitis                                   |               |                |               |

|                                                 |               |                |               |
|-------------------------------------------------|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Renal and urinary disorders                     |               |                |               |
| Acute Kidney Injury                             |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Musculoskeletal and connective tissue disorders |               |                |               |
| Back Pain                                       |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Osteoarthritis                                  |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Muscular Weakness                               |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Infections and infestations                     |               |                |               |
| Biliary Tract Infection                         |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Clostridium Difficile Infection                 |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Clostridium Difficile Colitis                   |               |                |               |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |

|                                                 |               |                |                |
|-------------------------------------------------|---------------|----------------|----------------|
| Enterococcal Infection                          |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Pneumonia                                       |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Meningitis                                      |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Sepsis                                          |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |               |                |                |
| Dehydration                                     |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 2 / 5 (40.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 3 / 3          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Hyperkalaemia                                   |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Hypoglycaemia                                   |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Hypokalaemia                                    |               |                |                |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Hyponatraemia                                   |               |                |                |

|                                                 |               |                |               |
|-------------------------------------------------|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |

| <b>Serious adverse events</b>                                       | P2 Arm A: 5 mg<br>Axitinib BID | P2 Arm B: 10 mg/kg<br>TRC105 Wkly + 5<br>mg Axitinib BID |  |
|---------------------------------------------------------------------|--------------------------------|----------------------------------------------------------|--|
| Total subjects affected by serious adverse events                   |                                |                                                          |  |
| subjects affected / exposed                                         | 27 / 74 (36.49%)               | 28 / 73 (38.36%)                                         |  |
| number of deaths (all causes)                                       | 3                              | 3                                                        |  |
| number of deaths resulting from adverse events                      |                                |                                                          |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                |                                                          |  |
| Bronchial Neoplasm                                                  |                                |                                                          |  |
| subjects affected / exposed                                         | 1 / 74 (1.35%)                 | 0 / 73 (0.00%)                                           |  |
| occurrences causally related to treatment / all                     | 0 / 1                          | 0 / 0                                                    |  |
| deaths causally related to treatment / all                          | 0 / 0                          | 0 / 0                                                    |  |
| Vascular disorders                                                  |                                |                                                          |  |
| Deep Vein Thrombosis                                                |                                |                                                          |  |
| subjects affected / exposed                                         | 0 / 74 (0.00%)                 | 0 / 73 (0.00%)                                           |  |
| occurrences causally related to treatment / all                     | 0 / 0                          | 0 / 0                                                    |  |
| deaths causally related to treatment / all                          | 0 / 0                          | 0 / 0                                                    |  |
| Hypertension                                                        |                                |                                                          |  |
| subjects affected / exposed                                         | 1 / 74 (1.35%)                 | 0 / 73 (0.00%)                                           |  |
| occurrences causally related to treatment / all                     | 1 / 1                          | 0 / 0                                                    |  |
| deaths causally related to treatment / all                          | 0 / 0                          | 0 / 0                                                    |  |
| General disorders and administration site conditions                |                                |                                                          |  |
| Chest pain                                                          |                                |                                                          |  |
| subjects affected / exposed                                         | 2 / 74 (2.70%)                 | 0 / 73 (0.00%)                                           |  |
| occurrences causally related to treatment / all                     | 1 / 2                          | 0 / 0                                                    |  |
| deaths causally related to treatment / all                          | 0 / 0                          | 0 / 0                                                    |  |
| Disease Progression                                                 |                                |                                                          |  |
| subjects affected / exposed                                         | 0 / 74 (0.00%)                 | 4 / 73 (5.48%)                                           |  |
| occurrences causally related to treatment / all                     | 0 / 0                          | 0 / 4                                                    |  |
| deaths causally related to treatment / all                          | 0 / 0                          | 0 / 4                                                    |  |
| Fatigue                                                             |                                |                                                          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Multi-organ Failure                             |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Reproductive system and breast disorders        |                |                |  |
| Pelvic Pain                                     |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 73 (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 |                |                |  |
| Pulmonary Embolism                              |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 2 / 73 (2.74%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pulmonary Haemorrhage                           |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Dyspnoea                                        |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Epistaxis                                       |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hypoxia                                         |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Pleural Effusion                                |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumothorax                                    |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory Failure                             |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| Vomiting                                        |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Psychiatric disorders                           |                |                |  |
| Confusional State                               |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Injury, poisoning and procedural complications  |                |                |  |
| Infusion Related Reaction                       |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Femur Fracture                                  |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Spinal Fracture                                 |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Cardiac disorders                               |                |                |  |
| Acute Heart Failure                             |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| Myocardial Infarction                           |                |                |  |
| subjects affected / exposed                     | 2 / 74 (2.70%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 1 / 2          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Nervous system disorders                        |                |                |  |
| Encephalopathy                                  |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 2 / 73 (2.74%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Epilepsy                                        |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hemiparesis                                     |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Haemorrhage Intracranial                        |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Migraine                                        |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Paraparesis                                     |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Posterior Reversible Encephalopathy Syndrome    |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Seizure                                         |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Headache                                        |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Blood and lymphatic system disorders            |                |                |  |
| Anaemia                                         |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 5 / 73 (6.85%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 4 / 8          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Eye disorders                                   |                |                |  |
| Retinal Vein Occlusion                          |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                      |                |                |  |
| Abdominal Pain                                  |                |                |  |
| subjects affected / exposed                     | 2 / 74 (2.70%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gallbladder Perforation                         |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Colitis                                         |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 74 (0.00%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Diarrhoea                                       |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Oesophageal Ulcer Haemorrhage                   |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Colonic Perforation                             |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal Perforation                    |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal Haemorrhage                    |                |                |  |
| subjects affected / exposed                     | 2 / 74 (2.70%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Lower Gastrointestinal Haemorrhage              |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pancreatitis                                    |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pyrexia                                         |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 74 (0.00%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hepatobiliary disorders                         |                |                |  |
| Liver Injury                                    |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cholecystitis                                   |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal and urinary disorders                     |                |                |  |
| Acute Kidney Injury                             |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 2 / 73 (2.74%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 3          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| Musculoskeletal and connective tissue disorders |                |                |  |
| Back Pain                                       |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 2 / 73 (2.74%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Osteoarthritis                                  |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Muscular Weakness                               |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Biliary Tract Infection                         |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Clostridium Difficile Infection                 |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Clostridium Difficile Colitis                   |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Enterococcal Infection                          |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumonia                                       |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Meningitis                                      |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Sepsis                                          |                |                |  |
| subjects affected / exposed                     | 2 / 74 (2.70%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Metabolism and nutrition disorders              |                |                |  |
| Dehydration                                     |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 3 / 73 (4.11%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 3 / 3          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hyperkalaemia                                   |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hypoglycaemia                                   |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hypokalaemia                                    |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hyponatraemia                                   |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| 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 %

| <b>Non-serious adverse events</b>                                   | P1b: 8 mg/kg<br>TRC105 Wkly + 5<br>mg Axitinib BID | P1b: 10 mg/kg<br>TRC105 Wkly + 5<br>mg Axitinib BID | P1b: 10 mg/kg<br>Wkly/15 mg/kg<br>q2wks TRC105 + 5<br>mg Axitinib BID |
|---------------------------------------------------------------------|----------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------------------------|
| Total subjects affected by non-serious adverse events               |                                                    |                                                     |                                                                       |
| subjects affected / exposed                                         | 3 / 3 (100.00%)                                    | 15 / 15 (100.00%)                                   | 5 / 5 (100.00%)                                                       |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                                    |                                                     |                                                                       |
| Basal Cell Carcinoma                                                |                                                    |                                                     |                                                                       |
| subjects affected / exposed                                         | 0 / 3 (0.00%)                                      | 0 / 15 (0.00%)                                      | 0 / 5 (0.00%)                                                         |
| occurrences (all)                                                   | 0                                                  | 0                                                   | 0                                                                     |
| Benign Neoplasm                                                     |                                                    |                                                     |                                                                       |
| subjects affected / exposed                                         | 0 / 3 (0.00%)                                      | 0 / 15 (0.00%)                                      | 0 / 5 (0.00%)                                                         |
| occurrences (all)                                                   | 0                                                  | 0                                                   | 0                                                                     |
| Breast Cancer                                                       |                                                    |                                                     |                                                                       |
| subjects affected / exposed                                         | 0 / 3 (0.00%)                                      | 0 / 15 (0.00%)                                      | 0 / 5 (0.00%)                                                         |
| occurrences (all)                                                   | 0                                                  | 0                                                   | 0                                                                     |
| Skin Papilloma                                                      |                                                    |                                                     |                                                                       |

|                                                  |                    |                     |                    |
|--------------------------------------------------|--------------------|---------------------|--------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Vascular disorders                               |                    |                     |                    |
| Aortic Aneurysm                                  |                    |                     |                    |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 15 (0.00%)      | 0 / 5 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Arteriosclerosis                                 |                    |                     |                    |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 15 (0.00%)      | 0 / 5 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Deep Vein Thrombosis                             |                    |                     |                    |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 15 (0.00%)      | 0 / 5 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Embolism                                         |                    |                     |                    |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 15 (0.00%)      | 0 / 5 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Flushing                                         |                    |                     |                    |
| subjects affected / exposed                      | 1 / 3 (33.33%)     | 0 / 15 (0.00%)      | 0 / 5 (0.00%)      |
| occurrences (all)                                | 1                  | 0                   | 0                  |
| Haematoma                                        |                    |                     |                    |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 15 (0.00%)      | 0 / 5 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Haemorrhage                                      |                    |                     |                    |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 15 (0.00%)      | 0 / 5 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Hot Flush                                        |                    |                     |                    |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 15 (0.00%)      | 0 / 5 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Hyperaemia                                       |                    |                     |                    |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 15 (0.00%)      | 0 / 5 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Hypertension                                     |                    |                     |                    |
| subjects affected / exposed                      | 2 / 3 (66.67%)     | 4 / 15 (26.67%)     | 4 / 5 (80.00%)     |
| occurrences (all)                                | 5                  | 8                   | 6                  |
| Hypotension                                      |                    |                     |                    |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 1 / 15 (6.67%)      | 1 / 5 (20.00%)     |
| occurrences (all)                                | 0                  | 1                   | 1                  |

|                                                                                  |                      |                      |                     |
|----------------------------------------------------------------------------------|----------------------|----------------------|---------------------|
| Orthostatic Hypotension<br>subjects affected / exposed<br>occurrences (all)      | 0 / 3 (0.00%)<br>0   | 0 / 15 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  |
| Thrombophlebitis Superficial<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0   | 0 / 15 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  |
| Surgical and medical procedures                                                  |                      |                      |                     |
| Colostomy<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 3 (0.00%)<br>0   | 0 / 15 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  |
| Tooth Extraction<br>subjects affected / exposed<br>occurrences (all)             | 0 / 3 (0.00%)<br>0   | 0 / 15 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  |
| Preventive Surgery<br>subjects affected / exposed<br>occurrences (all)           | 0 / 3 (0.00%)<br>0   | 1 / 15 (6.67%)<br>1  | 0 / 5 (0.00%)<br>0  |
| General disorders and administration<br>site conditions                          |                      |                      |                     |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)                     | 3 / 3 (100.00%)<br>5 | 2 / 15 (13.33%)<br>3 | 0 / 5 (0.00%)<br>0  |
| Catheter Site Pain<br>subjects affected / exposed<br>occurrences (all)           | 0 / 3 (0.00%)<br>0   | 0 / 15 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  |
| Catheter Site Swelling<br>subjects affected / exposed<br>occurrences (all)       | 0 / 3 (0.00%)<br>0   | 0 / 15 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  |
| Chest Discomfort<br>subjects affected / exposed<br>occurrences (all)             | 0 / 3 (0.00%)<br>0   | 1 / 15 (6.67%)<br>1  | 0 / 5 (0.00%)<br>0  |
| Chest Pain<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 3 (0.00%)<br>0   | 2 / 15 (13.33%)<br>4 | 0 / 5 (0.00%)<br>0  |
| Chills<br>subjects affected / exposed<br>occurrences (all)                       | 3 / 3 (100.00%)<br>4 | 1 / 15 (6.67%)<br>1  | 1 / 5 (20.00%)<br>1 |
| Drug Intolerance                                                                 |                      |                      |                     |

|                                       |                 |                 |                |
|---------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed           | 0 / 3 (0.00%)   | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                     | 0               | 0               | 0              |
| Facial Pain                           |                 |                 |                |
| subjects affected / exposed           | 0 / 3 (0.00%)   | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                     | 0               | 0               | 0              |
| Fatigue                               |                 |                 |                |
| subjects affected / exposed           | 3 / 3 (100.00%) | 9 / 15 (60.00%) | 4 / 5 (80.00%) |
| occurrences (all)                     | 4               | 28              | 6              |
| Feeling Cold                          |                 |                 |                |
| subjects affected / exposed           | 0 / 3 (0.00%)   | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)                     | 0               | 2               | 0              |
| Feeling Hot                           |                 |                 |                |
| subjects affected / exposed           | 0 / 3 (0.00%)   | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                     | 0               | 0               | 0              |
| General Physical Health Deterioration |                 |                 |                |
| subjects affected / exposed           | 0 / 3 (0.00%)   | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                     | 0               | 0               | 0              |
| Influenza Like Illness                |                 |                 |                |
| subjects affected / exposed           | 0 / 3 (0.00%)   | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)                     | 0               | 1               | 0              |
| Infusion Site Erythema                |                 |                 |                |
| subjects affected / exposed           | 0 / 3 (0.00%)   | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                     | 0               | 0               | 0              |
| Infusion Site Extravasation           |                 |                 |                |
| subjects affected / exposed           | 0 / 3 (0.00%)   | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                     | 0               | 0               | 0              |
| Injection Site Erythema               |                 |                 |                |
| subjects affected / exposed           | 0 / 3 (0.00%)   | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                     | 0               | 0               | 0              |
| Injection Site Haemorrhage            |                 |                 |                |
| subjects affected / exposed           | 0 / 3 (0.00%)   | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                     | 0               | 0               | 0              |
| Injection Site Mass                   |                 |                 |                |
| subjects affected / exposed           | 0 / 3 (0.00%)   | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                     | 0               | 0               | 0              |
| Local Swelling                        |                 |                 |                |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Malaise                     |                |                 |                |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 15 (0.00%)  | 1 / 5 (20.00%) |
| occurrences (all)           | 1              | 0               | 1              |
| Medical Device Site Bruise  |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Mucosal Inflammation        |                |                 |                |
| subjects affected / exposed | 1 / 3 (33.33%) | 7 / 15 (46.67%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 1              | 9               | 0              |
| Non-Cardiac Chest Pain      |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Oedema                      |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Oedema Peripheral           |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Pain                        |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Pyrexia                     |                |                 |                |
| subjects affected / exposed | 2 / 3 (66.67%) | 4 / 15 (26.67%) | 1 / 5 (20.00%) |
| occurrences (all)           | 8              | 5               | 1              |
| Temperature Intolerance     |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Thirst                      |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Gait Disturbance            |                |                 |                |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 2              | 0               | 0              |
| Immune system disorders     |                |                 |                |

|                                                                           |                    |                     |                    |
|---------------------------------------------------------------------------|--------------------|---------------------|--------------------|
| Hypersensitivity<br>subjects affected / exposed<br>occurrences (all)      | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Seasonal Allergy<br>subjects affected / exposed<br>occurrences (all)      | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Reproductive system and breast disorders                                  |                    |                     |                    |
| Breast Pain<br>subjects affected / exposed<br>occurrences (all)           | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Erectile Dysfunction<br>subjects affected / exposed<br>occurrences (all)  | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Genital Discharge<br>subjects affected / exposed<br>occurrences (all)     | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Gynaecomastia<br>subjects affected / exposed<br>occurrences (all)         | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Nipple Pain<br>subjects affected / exposed<br>occurrences (all)           | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Pelvic Pain<br>subjects affected / exposed<br>occurrences (all)           | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Prostatic Obstruction<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Scrotal Pain<br>subjects affected / exposed<br>occurrences (all)          | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Vaginal Lesion<br>subjects affected / exposed<br>occurrences (all)        | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Vulvovaginal Pain                                                         |                    |                     |                    |

|                                                 |                |                  |                 |
|-------------------------------------------------|----------------|------------------|-----------------|
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 15 (0.00%)   | 0 / 5 (0.00%)   |
| occurrences (all)                               | 0              | 0                | 0               |
| Respiratory, thoracic and mediastinal disorders |                |                  |                 |
| Choking Sensation                               |                |                  |                 |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 15 (0.00%)   | 0 / 5 (0.00%)   |
| occurrences (all)                               | 0              | 0                | 0               |
| Cough                                           |                |                  |                 |
| subjects affected / exposed                     | 1 / 3 (33.33%) | 5 / 15 (33.33%)  | 1 / 5 (20.00%)  |
| occurrences (all)                               | 1              | 6                | 1               |
| Dry Throat                                      |                |                  |                 |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 15 (0.00%)   | 0 / 5 (0.00%)   |
| occurrences (all)                               | 0              | 0                | 0               |
| Dysphonia                                       |                |                  |                 |
| subjects affected / exposed                     | 1 / 3 (33.33%) | 6 / 15 (40.00%)  | 3 / 5 (60.00%)  |
| occurrences (all)                               | 1              | 13               | 3               |
| Dyspnoea                                        |                |                  |                 |
| subjects affected / exposed                     | 1 / 3 (33.33%) | 1 / 15 (6.67%)   | 0 / 5 (0.00%)   |
| occurrences (all)                               | 1              | 1                | 0               |
| Dyspnoea Exertional                             |                |                  |                 |
| subjects affected / exposed                     | 1 / 3 (33.33%) | 2 / 15 (13.33%)  | 0 / 5 (0.00%)   |
| occurrences (all)                               | 4              | 2                | 0               |
| Epistaxis                                       |                |                  |                 |
| subjects affected / exposed                     | 2 / 3 (66.67%) | 13 / 15 (86.67%) | 5 / 5 (100.00%) |
| occurrences (all)                               | 2              | 23               | 6               |
| Haemoptysis                                     |                |                  |                 |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 15 (0.00%)   | 0 / 5 (0.00%)   |
| occurrences (all)                               | 0              | 0                | 0               |
| Hiccups                                         |                |                  |                 |
| subjects affected / exposed                     | 1 / 3 (33.33%) | 0 / 15 (0.00%)   | 0 / 5 (0.00%)   |
| occurrences (all)                               | 1              | 0                | 0               |
| Hypoxia                                         |                |                  |                 |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 2 / 15 (13.33%)  | 0 / 5 (0.00%)   |
| occurrences (all)                               | 0              | 2                | 0               |
| Increased Upper Airway Secretion                |                |                  |                 |

|                              |                |                |                |
|------------------------------|----------------|----------------|----------------|
| subjects affected / exposed  | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)            | 0              | 0              | 0              |
| Nasal Congestion             |                |                |                |
| subjects affected / exposed  | 0 / 3 (0.00%)  | 1 / 15 (6.67%) | 0 / 5 (0.00%)  |
| occurrences (all)            | 0              | 1              | 0              |
| Nasal Dryness                |                |                |                |
| subjects affected / exposed  | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)            | 0              | 0              | 0              |
| Nasal Septum Disorder        |                |                |                |
| subjects affected / exposed  | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)            | 0              | 0              | 0              |
| Nasal Septum Perforation     |                |                |                |
| subjects affected / exposed  | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)            | 0              | 0              | 0              |
| Nasal Septum Ulceration      |                |                |                |
| subjects affected / exposed  | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)            | 0              | 0              | 0              |
| Nasal Ulcer                  |                |                |                |
| subjects affected / exposed  | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)            | 0              | 0              | 0              |
| Oropharyngeal Pain           |                |                |                |
| subjects affected / exposed  | 0 / 3 (0.00%)  | 1 / 15 (6.67%) | 0 / 5 (0.00%)  |
| occurrences (all)            | 0              | 1              | 0              |
| Pleural Effusion             |                |                |                |
| subjects affected / exposed  | 0 / 3 (0.00%)  | 1 / 15 (6.67%) | 1 / 5 (20.00%) |
| occurrences (all)            | 0              | 1              | 1              |
| Productive Cough             |                |                |                |
| subjects affected / exposed  | 1 / 3 (33.33%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)            | 1              | 0              | 0              |
| Pulmonary Embolism           |                |                |                |
| subjects affected / exposed  | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all)            | 0              | 0              | 1              |
| Respiratory Tract Congestion |                |                |                |
| subjects affected / exposed  | 1 / 3 (33.33%) | 1 / 15 (6.67%) | 0 / 5 (0.00%)  |
| occurrences (all)            | 1              | 1              | 0              |
| Rhinitis Allergic            |                |                |                |

|                                      |                |                 |                |
|--------------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed          | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                    | 0              | 0               | 0              |
| Rhinorrhoea                          |                |                 |                |
| subjects affected / exposed          | 1 / 3 (33.33%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                    | 1              | 0               | 0              |
| Sinus Congestion                     |                |                 |                |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 1 / 5 (20.00%) |
| occurrences (all)                    | 0              | 0               | 1              |
| Sleep Apnoea Syndrome                |                |                 |                |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                    | 0              | 0               | 0              |
| Tachypnoea                           |                |                 |                |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                    | 0              | 0               | 0              |
| Upper Respiratory Tract Inflammation |                |                 |                |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                    | 0              | 0               | 0              |
| Upper-airway Cough Syndrome          |                |                 |                |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)                    | 0              | 1               | 0              |
| Wheezing                             |                |                 |                |
| subjects affected / exposed          | 1 / 3 (33.33%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                    | 1              | 0               | 0              |
| Psychiatric disorders                |                |                 |                |
| Agitation                            |                |                 |                |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)                    | 0              | 1               | 0              |
| Anxiety                              |                |                 |                |
| subjects affected / exposed          | 1 / 3 (33.33%) | 2 / 15 (13.33%) | 0 / 5 (0.00%)  |
| occurrences (all)                    | 1              | 2               | 0              |
| Confusional State                    |                |                 |                |
| subjects affected / exposed          | 1 / 3 (33.33%) | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)                    | 1              | 1               | 0              |
| Delirium                             |                |                 |                |

|                                                 |                |                 |                |
|-------------------------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)                               | 0              | 1               | 0              |
| Depression                                      |                |                 |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)                               | 0              | 1               | 0              |
| Insomnia                                        |                |                 |                |
| subjects affected / exposed                     | 1 / 3 (33.33%) | 3 / 15 (20.00%) | 1 / 5 (20.00%) |
| occurrences (all)                               | 1              | 3               | 1              |
| Mental Status Changes                           |                |                 |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0              |
| Investigations                                  |                |                 |                |
| Activated Partial Thromboplastin Time Prolonged |                |                 |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0              |
| Alanine Aminotransferase Increased              |                |                 |                |
| subjects affected / exposed                     | 1 / 3 (33.33%) | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)                               | 1              | 1               | 0              |
| Aspartate Aminotransferase Increased            |                |                 |                |
| subjects affected / exposed                     | 1 / 3 (33.33%) | 3 / 15 (20.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 1              | 7               | 0              |
| Blood Alkaline Phosphatase Increased            |                |                 |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)                               | 0              | 1               | 0              |
| Blood Amylase Increased                         |                |                 |                |
| subjects affected / exposed                     | 1 / 3 (33.33%) | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)                               | 2              | 1               | 0              |
| Blood Bilirubin Increased                       |                |                 |                |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                               | 0              | 0               | 0              |
| Blood Creatinine Increased                      |                |                 |                |
| subjects affected / exposed                     | 1 / 3 (33.33%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                               | 1              | 0               | 0              |
| Blood Pressure Increased                        |                |                 |                |

|                                             |               |                |               |
|---------------------------------------------|---------------|----------------|---------------|
| subjects affected / exposed                 | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)                           | 0             | 0              | 0             |
| Blood Thyroid Stimulating Hormone Decreased |               |                |               |
| subjects affected / exposed                 | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)                           | 0             | 0              | 0             |
| Blood Thyroid Stimulating Hormone Increased |               |                |               |
| subjects affected / exposed                 | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)                           | 0             | 0              | 0             |
| Blood Urea Increased                        |               |                |               |
| subjects affected / exposed                 | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)                           | 0             | 0              | 0             |
| Cardiac Murmur                              |               |                |               |
| subjects affected / exposed                 | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)                           | 0             | 0              | 0             |
| Electrocardiogram QT Prolonged              |               |                |               |
| subjects affected / exposed                 | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)                           | 0             | 0              | 0             |
| Epidermal Growth Factor Receptor Increased  |               |                |               |
| subjects affected / exposed                 | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)                           | 0             | 0              | 0             |
| Gamma-Glutamyltransferase Increased         |               |                |               |
| subjects affected / exposed                 | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)                           | 0             | 0              | 0             |
| Glucose Urine Present                       |               |                |               |
| subjects affected / exposed                 | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)                           | 0             | 0              | 0             |
| Haemoglobin Increased                       |               |                |               |
| subjects affected / exposed                 | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)                           | 0             | 0              | 0             |
| International Normalised Ratio Increased    |               |                |               |
| subjects affected / exposed                 | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)                           | 0             | 0              | 0             |
| Iron Binding Capacity Total Decreased       |               |                |               |

|                                                     |                |                 |                |
|-----------------------------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed                         | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                                   | 0              | 0               | 0              |
| Lipase Increased                                    |                |                 |                |
| subjects affected / exposed                         | 1 / 3 (33.33%) | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)                                   | 2              | 2               | 0              |
| Liver Function Test Abnormal                        |                |                 |                |
| subjects affected / exposed                         | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                                   | 0              | 0               | 0              |
| Liver Function Test Increased                       |                |                 |                |
| subjects affected / exposed                         | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)                                   | 0              | 1               | 0              |
| Lymphocyte Count Decreased                          |                |                 |                |
| subjects affected / exposed                         | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                                   | 0              | 0               | 0              |
| Mycobacterium Tuberculosis<br>Complex Test Positive |                |                 |                |
| subjects affected / exposed                         | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                                   | 0              | 0               | 0              |
| Red Blood Cells Urine                               |                |                 |                |
| subjects affected / exposed                         | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                                   | 0              | 0               | 0              |
| Transaminases Increased                             |                |                 |                |
| subjects affected / exposed                         | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                                   | 0              | 0               | 0              |
| Vitamin D Decreased                                 |                |                 |                |
| subjects affected / exposed                         | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                                   | 0              | 0               | 0              |
| Weight Decreased                                    |                |                 |                |
| subjects affected / exposed                         | 0 / 3 (0.00%)  | 3 / 15 (20.00%) | 2 / 5 (40.00%) |
| occurrences (all)                                   | 0              | 4               | 7              |
| Weight Increased                                    |                |                 |                |
| subjects affected / exposed                         | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)                                   | 0              | 1               | 0              |
| White Blood Cell Count Decreased                    |                |                 |                |
| subjects affected / exposed                         | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                                   | 0              | 0               | 0              |

|                                                                               |                     |                      |                    |
|-------------------------------------------------------------------------------|---------------------|----------------------|--------------------|
| White Blood Cells Urine<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0 |
| Food Intolerance<br>subjects affected / exposed<br>occurrences (all)          | 0 / 3 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0 |
| Gout<br>subjects affected / exposed<br>occurrences (all)                      | 2 / 3 (66.67%)<br>5 | 0 / 15 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0 |
| Injury, poisoning and procedural complications                                |                     |                      |                    |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 3 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0 |
| Fall<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 3 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0 |
| Head Injury<br>subjects affected / exposed<br>occurrences (all)               | 0 / 3 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0 |
| Incisional Hernia<br>subjects affected / exposed<br>occurrences (all)         | 0 / 3 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0 |
| Infusion Related Reaction<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0  | 3 / 15 (20.00%)<br>3 | 0 / 5 (0.00%)<br>0 |
| Joint Injury<br>subjects affected / exposed<br>occurrences (all)              | 0 / 3 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0 |
| Laceration<br>subjects affected / exposed<br>occurrences (all)                | 0 / 3 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0 |
| Limb Injury<br>subjects affected / exposed<br>occurrences (all)               | 0 / 3 (0.00%)<br>0  | 1 / 15 (6.67%)<br>1  | 0 / 5 (0.00%)<br>0 |
| Lower Limb Fracture                                                           |                     |                      |                    |

|                             |               |                |               |
|-----------------------------|---------------|----------------|---------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Muscle Strain               |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Post Procedural Discomfort  |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Procedural pain             |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Rib Fracture                |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Road Traffic Accident       |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Skin Abrasion               |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Sternal Fracture            |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Thermal Burn                |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Wound                       |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Wound Complication          |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Wound Dehiscence            |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Cardiac disorders           |               |                |               |

|                                                                                  |                    |                     |                    |
|----------------------------------------------------------------------------------|--------------------|---------------------|--------------------|
| Acute Coronary Syndrome<br>subjects affected / exposed<br>occurrences (all)      | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Angina Pectoris<br>subjects affected / exposed<br>occurrences (all)              | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Arrhythmia<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Bradycardia<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 3 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 | 0 / 5 (0.00%)<br>0 |
| Bundle Branch Block Right<br>subjects affected / exposed<br>occurrences (all)    | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Cardiac Disorder<br>subjects affected / exposed<br>occurrences (all)             | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Cardiac Failure<br>subjects affected / exposed<br>occurrences (all)              | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Cardiac Failure Acute<br>subjects affected / exposed<br>occurrences (all)        | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Coronary Artery Disease<br>subjects affected / exposed<br>occurrences (all)      | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Coronary Artery Thrombosis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Diastolic Dysfunction<br>subjects affected / exposed<br>occurrences (all)        | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Left Ventricular Dysfunction<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |

|                                                                                         |                    |                     |                     |
|-----------------------------------------------------------------------------------------|--------------------|---------------------|---------------------|
| Mitral Valve Incompetence<br>subjects affected / exposed<br>occurrences (all)           | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Pericardial Effusion<br>subjects affected / exposed<br>occurrences (all)                | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Sinus Bradycardia<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Sinus Tachycardia<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Supraventricular Extrasystoles<br>subjects affected / exposed<br>occurrences (all)      | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 3 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 | 1 / 5 (20.00%)<br>1 |
| Tricuspid Valve Incompetence<br>subjects affected / exposed<br>occurrences (all)        | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Ventricular Extrasystoles<br>subjects affected / exposed<br>occurrences (all)           | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Wandering Pacemaker<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 3 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 | 0 / 5 (0.00%)<br>0  |
| Nervous system disorders<br>Amnesia<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Balance Disorder                                                                        |                    |                     |                     |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Burning Sensation           |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Cerebrovascular Accident    |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Cognitive Disorder          |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Convulsion                  |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Disturbance In Attention    |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Dizziness                   |                |                 |                |
| subjects affected / exposed | 1 / 3 (33.33%) | 3 / 15 (20.00%) | 1 / 5 (20.00%) |
| occurrences (all)           | 1              | 3               | 1              |
| Dizziness Postural          |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Dysaesthesia                |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Dysgeusia                   |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 1 / 5 (20.00%) |
| occurrences (all)           | 0              | 0               | 1              |
| Dyskinesia                  |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Encephalopathy              |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Headache                    |                |                 |                |

|                             |                 |                  |                |
|-----------------------------|-----------------|------------------|----------------|
| subjects affected / exposed | 3 / 3 (100.00%) | 10 / 15 (66.67%) | 2 / 5 (40.00%) |
| occurrences (all)           | 4               | 17               | 2              |
| Hyperaesthesia              |                 |                  |                |
| subjects affected / exposed | 0 / 3 (0.00%)   | 0 / 15 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0                | 0              |
| Hypersomnia                 |                 |                  |                |
| subjects affected / exposed | 0 / 3 (0.00%)   | 0 / 15 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0                | 0              |
| Hypoaesthesia               |                 |                  |                |
| subjects affected / exposed | 0 / 3 (0.00%)   | 0 / 15 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0                | 0              |
| Hypotonia                   |                 |                  |                |
| subjects affected / exposed | 0 / 3 (0.00%)   | 0 / 15 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0                | 0              |
| Lethargy                    |                 |                  |                |
| subjects affected / exposed | 2 / 3 (66.67%)  | 1 / 15 (6.67%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 2               | 1                | 0              |
| Memory Impairment           |                 |                  |                |
| subjects affected / exposed | 0 / 3 (0.00%)   | 0 / 15 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0                | 0              |
| Mental Impairment           |                 |                  |                |
| subjects affected / exposed | 0 / 3 (0.00%)   | 0 / 15 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0                | 0              |
| Metabolic Encephalopathy    |                 |                  |                |
| subjects affected / exposed | 0 / 3 (0.00%)   | 0 / 15 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0                | 0              |
| Migraine                    |                 |                  |                |
| subjects affected / exposed | 0 / 3 (0.00%)   | 0 / 15 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0                | 0              |
| Neuropathy Peripheral       |                 |                  |                |
| subjects affected / exposed | 0 / 3 (0.00%)   | 1 / 15 (6.67%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 1                | 0              |
| Paraesthesia                |                 |                  |                |
| subjects affected / exposed | 0 / 3 (0.00%)   | 1 / 15 (6.67%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 2                | 0              |
| Paresis                     |                 |                  |                |

|                                      |                |                 |                |
|--------------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed          | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                    | 0              | 0               | 0              |
| Peripheral Sensory Neuropathy        |                |                 |                |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                    | 0              | 0               | 0              |
| Presyncope                           |                |                 |                |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                    | 0              | 0               | 0              |
| Sciatica                             |                |                 |                |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                    | 0              | 0               | 0              |
| Sinus Headache                       |                |                 |                |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                    | 0              | 0               | 0              |
| Spinal Cord Compression              |                |                 |                |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                    | 0              | 0               | 0              |
| Syncope                              |                |                 |                |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                    | 0              | 0               | 0              |
| Tremor                               |                |                 |                |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)                    | 0              | 1               | 0              |
| Somnolence                           |                |                 |                |
| subjects affected / exposed          | 1 / 3 (33.33%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                    | 2              | 0               | 0              |
| Speech Disorder                      |                |                 |                |
| subjects affected / exposed          | 1 / 3 (33.33%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                    | 1              | 0               | 0              |
| Ageusia                              |                |                 |                |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 2 / 5 (40.00%) |
| occurrences (all)                    | 0              | 0               | 2              |
| Blood and lymphatic system disorders |                |                 |                |
| Anaemia                              |                |                 |                |
| subjects affected / exposed          | 1 / 3 (33.33%) | 4 / 15 (26.67%) | 1 / 5 (20.00%) |
| occurrences (all)                    | 1              | 17              | 4              |

|                             |               |                |               |
|-----------------------------|---------------|----------------|---------------|
| Leukocytosis                |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Leukopenia                  |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Microcytic Anaemia          |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Neutropenia                 |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Polycythaemia               |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Thrombocytosis              |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Haemolytic Anaemia          |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 15 (6.67%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 1              | 0             |
| Ear and labyrinth disorders |               |                |               |
| Cerumen Impaction           |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Ear Discomfort              |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Ear Pain                    |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Hearing Impaired            |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Hypoacusis                  |               |                |               |

|                               |                |                 |                |
|-------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed   | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)             | 0              | 1               | 0              |
| Tinnitus                      |                |                 |                |
| subjects affected / exposed   | 1 / 3 (33.33%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)             | 1              | 0               | 0              |
| Tympanic Membrane Perforation |                |                 |                |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)             | 0              | 0               | 0              |
| Vertigo                       |                |                 |                |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)             | 0              | 0               | 0              |
| Ear Haemorrhage               |                |                 |                |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 1 / 5 (20.00%) |
| occurrences (all)             | 0              | 0               | 1              |
| Eye disorders                 |                |                 |                |
| Cataract                      |                |                 |                |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)             | 0              | 0               | 0              |
| Eye Discharge                 |                |                 |                |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)             | 0              | 0               | 0              |
| Eye Pain                      |                |                 |                |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)             | 0              | 0               | 0              |
| Lacrimation increased         |                |                 |                |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)             | 0              | 1               | 0              |
| Periorbital Oedema            |                |                 |                |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 2 / 15 (13.33%) | 0 / 5 (0.00%)  |
| occurrences (all)             | 0              | 2               | 0              |
| Photophobia                   |                |                 |                |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)             | 0              | 0               | 0              |
| Retinal Vein Occlusion        |                |                 |                |
| subjects affected / exposed   | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)             | 0              | 0               | 0              |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| Vision Blurred              |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Visual Impairment           |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Ocular Hyperaemia           |                |                 |                |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 1              | 0               | 0              |
| Gastrointestinal disorders  |                |                 |                |
| Abdominal Discomfort        |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Abdominal Distension        |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 3 / 15 (20.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 5               | 0              |
| Abdominal Hernia            |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Abdominal Pain              |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 5 / 15 (33.33%) | 1 / 5 (20.00%) |
| occurrences (all)           | 0              | 7               | 2              |
| Abdominal Pain Lower        |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Abdominal Pain Upper        |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Abdominal Tenderness        |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Anorectal Discomfort        |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Ascites                     |                |                 |                |

|                             |                 |                  |                |
|-----------------------------|-----------------|------------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%)   | 1 / 15 (6.67%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 1                | 0              |
| Cheilitis                   |                 |                  |                |
| subjects affected / exposed | 0 / 3 (0.00%)   | 0 / 15 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0                | 0              |
| Colitis                     |                 |                  |                |
| subjects affected / exposed | 0 / 3 (0.00%)   | 0 / 15 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0                | 0              |
| Constipation                |                 |                  |                |
| subjects affected / exposed | 1 / 3 (33.33%)  | 5 / 15 (33.33%)  | 2 / 5 (40.00%) |
| occurrences (all)           | 2               | 7                | 2              |
| Dental Caries               |                 |                  |                |
| subjects affected / exposed | 0 / 3 (0.00%)   | 0 / 15 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0                | 0              |
| Diarrhoea                   |                 |                  |                |
| subjects affected / exposed | 3 / 3 (100.00%) | 11 / 15 (73.33%) | 4 / 5 (80.00%) |
| occurrences (all)           | 8               | 32               | 14             |
| Diverticulum                |                 |                  |                |
| subjects affected / exposed | 0 / 3 (0.00%)   | 0 / 15 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0                | 0              |
| Dry Mouth                   |                 |                  |                |
| subjects affected / exposed | 0 / 3 (0.00%)   | 1 / 15 (6.67%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 1                | 0              |
| Dyskinesia Oesophageal      |                 |                  |                |
| subjects affected / exposed | 0 / 3 (0.00%)   | 0 / 15 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0                | 0              |
| Dyspepsia                   |                 |                  |                |
| subjects affected / exposed | 1 / 3 (33.33%)  | 1 / 15 (6.67%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 1               | 1                | 0              |
| Dysphagia                   |                 |                  |                |
| subjects affected / exposed | 0 / 3 (0.00%)   | 1 / 15 (6.67%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 1                | 0              |
| Enteritis                   |                 |                  |                |
| subjects affected / exposed | 0 / 3 (0.00%)   | 0 / 15 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0                | 0              |
| Faecal Incontinence         |                 |                  |                |

|                                  |                |                 |                 |
|----------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed      | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)   |
| occurrences (all)                | 0              | 0               | 0               |
| Faeces Discoloured               |                |                 |                 |
| subjects affected / exposed      | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)   |
| occurrences (all)                | 0              | 0               | 0               |
| Faeces Pale                      |                |                 |                 |
| subjects affected / exposed      | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)   |
| occurrences (all)                | 0              | 0               | 0               |
| Flatulence                       |                |                 |                 |
| subjects affected / exposed      | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)   |
| occurrences (all)                | 0              | 0               | 0               |
| Gastritis                        |                |                 |                 |
| subjects affected / exposed      | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)   |
| occurrences (all)                | 0              | 0               | 0               |
| Gastrointestinal Pain            |                |                 |                 |
| subjects affected / exposed      | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)   |
| occurrences (all)                | 0              | 0               | 0               |
| Gastrooesophageal Reflux Disease |                |                 |                 |
| subjects affected / exposed      | 0 / 3 (0.00%)  | 2 / 15 (13.33%) | 0 / 5 (0.00%)   |
| occurrences (all)                | 0              | 3               | 0               |
| Gingival Bleeding                |                |                 |                 |
| subjects affected / exposed      | 2 / 3 (66.67%) | 7 / 15 (46.67%) | 5 / 5 (100.00%) |
| occurrences (all)                | 3              | 11              | 5               |
| Gingival Pain                    |                |                 |                 |
| subjects affected / exposed      | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)   |
| occurrences (all)                | 0              | 0               | 0               |
| Glossitis                        |                |                 |                 |
| subjects affected / exposed      | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)   |
| occurrences (all)                | 0              | 0               | 0               |
| Glossodynia                      |                |                 |                 |
| subjects affected / exposed      | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 1 / 5 (20.00%)  |
| occurrences (all)                | 0              | 0               | 1               |
| Haematemesis                     |                |                 |                 |
| subjects affected / exposed      | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)   |
| occurrences (all)                | 0              | 1               | 0               |
| Haematochezia                    |                |                 |                 |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Haemorrhoidal Haemorrhage   |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Haemorrhoids                |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 2 / 15 (13.33%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 2               | 0              |
| Hiatus Hernia               |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Large Intestine Perforation |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Melaena                     |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Mesenteric Vein Thrombosis  |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Mouth Haemorrhage           |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Mouth Ulceration            |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Nausea                      |                |                 |                |
| subjects affected / exposed | 1 / 3 (33.33%) | 9 / 15 (60.00%) | 4 / 5 (80.00%) |
| occurrences (all)           | 1              | 16              | 6              |
| Oesophageal Ulcer           |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Oesophagitis                |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Oral Discomfort             |                |                 |                |

|                             |               |                |                |
|-----------------------------|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Oral Disorder               |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Oral Dysaesthesia           |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Oral Mucosal Erythema       |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Oral Pain                   |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 15 (6.67%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0             | 1              | 0              |
| Paraesthesia Oral           |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Peptic Ulcer                |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Periodontal Disease         |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all)           | 0             | 0              | 1              |
| Proctalgia                  |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Rectal Haemorrhage          |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Retching                    |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Salivary Hypersecretion     |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Stomatitis                  |               |                |                |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 3 / 5 (60.00%) |
| occurrences (all)           | 0              | 5               | 6              |
| Swollen Tongue              |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Toothache                   |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Vomiting                    |                |                 |                |
| subjects affected / exposed | 1 / 3 (33.33%) | 5 / 15 (33.33%) | 4 / 5 (80.00%) |
| occurrences (all)           | 1              | 8               | 6              |
| Duodenitis                  |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Impaired Gastric Emptying   |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 4               | 0              |
| Periodontitis               |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Hepatobiliary disorders     |                |                 |                |
| Bile Duct Stenosis          |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Cholelithiasis              |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Gallbladder Pain            |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Hepatitis                   |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Liver Disorder              |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |

|                                        |                |                 |                |
|----------------------------------------|----------------|-----------------|----------------|
| Skin and subcutaneous tissue disorders |                |                 |                |
| Acne                                   |                |                 |                |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                      | 0              | 0               | 0              |
| Actinic Keratosis                      |                |                 |                |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                      | 0              | 0               | 0              |
| Alopecia                               |                |                 |                |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                      | 0              | 0               | 0              |
| Blister                                |                |                 |                |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                      | 0              | 0               | 0              |
| Decubitus Ulcer                        |                |                 |                |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)                      | 0              | 1               | 0              |
| Dermatitis                             |                |                 |                |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 1 / 5 (20.00%) |
| occurrences (all)                      | 0              | 0               | 1              |
| Dermatitis Acneiform                   |                |                 |                |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 3 / 15 (20.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                      | 0              | 4               | 0              |
| Dermatitis Bullous                     |                |                 |                |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                      | 0              | 0               | 0              |
| Dry Skin                               |                |                 |                |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                      | 0              | 0               | 0              |
| Erythema                               |                |                 |                |
| subjects affected / exposed            | 0 / 3 (0.00%)  | 2 / 15 (13.33%) | 0 / 5 (0.00%)  |
| occurrences (all)                      | 0              | 3               | 0              |
| Hyperhidrosis                          |                |                 |                |
| subjects affected / exposed            | 1 / 3 (33.33%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                      | 1              | 0               | 0              |
| Hyperkeratosis                         |                |                 |                |

|                                             |                |                 |                |
|---------------------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed                 | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                           | 0              | 0               | 0              |
| Ingrowing Nail                              |                |                 |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                           | 0              | 0               | 0              |
| Livedo Reticularis                          |                |                 |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                           | 0              | 0               | 0              |
| Nail Discolouration                         |                |                 |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                           | 0              | 0               | 0              |
| Night Sweats                                |                |                 |                |
| subjects affected / exposed                 | 2 / 3 (66.67%) | 3 / 15 (20.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                           | 2              | 3               | 0              |
| Palmar-plantar Erythrodysaesthesia Syndrome |                |                 |                |
| subjects affected / exposed                 | 1 / 3 (33.33%) | 5 / 15 (33.33%) | 2 / 5 (40.00%) |
| occurrences (all)                           | 2              | 10              | 4              |
| Palmoplantar Keratoderma                    |                |                 |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                           | 0              | 0               | 0              |
| Photosensitivity Reaction                   |                |                 |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                           | 0              | 0               | 0              |
| Pruritus                                    |                |                 |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                           | 0              | 0               | 0              |
| Purpura                                     |                |                 |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                           | 0              | 0               | 0              |
| Rash                                        |                |                 |                |
| subjects affected / exposed                 | 1 / 3 (33.33%) | 3 / 15 (20.00%) | 1 / 5 (20.00%) |
| occurrences (all)                           | 1              | 4               | 1              |
| Rash Erythematous                           |                |                 |                |
| subjects affected / exposed                 | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)                           | 0              | 0               | 0              |

|                             |                |                |               |
|-----------------------------|----------------|----------------|---------------|
| Rash Macular                |                |                |               |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Rash Maculo-papular         |                |                |               |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 15 (6.67%) | 0 / 5 (0.00%) |
| occurrences (all)           | 1              | 1              | 0             |
| Rash Pruritic               |                |                |               |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Rosacea                     |                |                |               |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Scab                        |                |                |               |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Skin Discolouration         |                |                |               |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Skin Erosion                |                |                |               |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Skin Exfoliation            |                |                |               |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Skin Hyperpigmentation      |                |                |               |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Skin Lesion                 |                |                |               |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 15 (6.67%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 1              | 0             |
| Skin Ulcer                  |                |                |               |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Subcutaneous Nodule         |                |                |               |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |

|                             |                |                |               |
|-----------------------------|----------------|----------------|---------------|
| Swelling Face               |                |                |               |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Telangiectasia              |                |                |               |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Petechiae                   |                |                |               |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 15 (6.67%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 1              | 0             |
| Renal and urinary disorders |                |                |               |
| Acute Kidney Injury         |                |                |               |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 1              | 0              | 0             |
| Bladder Spasm               |                |                |               |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Dysuria                     |                |                |               |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Glycosuria                  |                |                |               |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Haematuria                  |                |                |               |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 15 (6.67%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 1              | 0             |
| Hydronephrosis              |                |                |               |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Micturition Urgency         |                |                |               |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Nephrolithiasis             |                |                |               |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0              | 0             |
| Pollakiuria                 |                |                |               |

|                              |               |                 |                |
|------------------------------|---------------|-----------------|----------------|
| subjects affected / exposed  | 0 / 3 (0.00%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)            | 0             | 0               | 0              |
| Proteinuria                  |               |                 |                |
| subjects affected / exposed  | 0 / 3 (0.00%) | 2 / 15 (13.33%) | 0 / 5 (0.00%)  |
| occurrences (all)            | 0             | 3               | 0              |
| Renal Failure                |               |                 |                |
| subjects affected / exposed  | 0 / 3 (0.00%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)            | 0             | 0               | 0              |
| Urethral Meatus Stenosis     |               |                 |                |
| subjects affected / exposed  | 0 / 3 (0.00%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)            | 0             | 0               | 0              |
| Urinary Incontinence         |               |                 |                |
| subjects affected / exposed  | 0 / 3 (0.00%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)            | 0             | 0               | 0              |
| Urinary Retention            |               |                 |                |
| subjects affected / exposed  | 0 / 3 (0.00%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)            | 0             | 0               | 0              |
| Urinary Tract Pain           |               |                 |                |
| subjects affected / exposed  | 0 / 3 (0.00%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)            | 0             | 0               | 0              |
| Incontinence                 |               |                 |                |
| subjects affected / exposed  | 0 / 3 (0.00%) | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)            | 0             | 1               | 0              |
| Endocrine disorders          |               |                 |                |
| Adrenal Insufficiency        |               |                 |                |
| subjects affected / exposed  | 0 / 3 (0.00%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)            | 0             | 0               | 0              |
| Hypercalcaemia of malignancy |               |                 |                |
| subjects affected / exposed  | 0 / 3 (0.00%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)            | 0             | 0               | 0              |
| Hyperthyroidism              |               |                 |                |
| subjects affected / exposed  | 0 / 3 (0.00%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)            | 0             | 0               | 0              |
| Hypothyroidism               |               |                 |                |
| subjects affected / exposed  | 0 / 3 (0.00%) | 0 / 15 (0.00%)  | 1 / 5 (20.00%) |
| occurrences (all)            | 0             | 0               | 1              |

|                                                                                |                    |                      |                     |
|--------------------------------------------------------------------------------|--------------------|----------------------|---------------------|
| Thyroid Disorder<br>subjects affected / exposed<br>occurrences (all)           | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  |
| Musculoskeletal and connective tissue disorders                                |                    |                      |                     |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 3 (0.00%)<br>0 | 2 / 15 (13.33%)<br>3 | 0 / 5 (0.00%)<br>0  |
| Back Pain<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 3 (0.00%)<br>0 | 3 / 15 (20.00%)<br>3 | 1 / 5 (20.00%)<br>2 |
| Bone Pain<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 3 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1  | 0 / 5 (0.00%)<br>0  |
| Flank Pain<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  |
| Groin Pain<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  |
| Inguinal Mass<br>subjects affected / exposed<br>occurrences (all)              | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  |
| Joint Swelling<br>subjects affected / exposed<br>occurrences (all)             | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  |
| Muscle Spasms<br>subjects affected / exposed<br>occurrences (all)              | 0 / 3 (0.00%)<br>0 | 2 / 15 (13.33%)<br>2 | 0 / 5 (0.00%)<br>0  |
| Muscular Weakness<br>subjects affected / exposed<br>occurrences (all)          | 0 / 3 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1  | 0 / 5 (0.00%)<br>0  |
| Musculoskeletal Chest Pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  |
| Musculoskeletal Pain                                                           |                    |                      |                     |

|                             |               |                 |               |
|-----------------------------|---------------|-----------------|---------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 15 (6.67%)  | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 2               | 0             |
| Myalgia                     |               |                 |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 15 (6.67%)  | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 1               | 0             |
| Neck Pain                   |               |                 |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Osteoarthritis              |               |                 |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Osteoporosis                |               |                 |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Pain In Extremity           |               |                 |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 5 / 15 (33.33%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 6               | 0             |
| Pain In Jaw                 |               |                 |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 15 (6.67%)  | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 2               | 0             |
| Pathological Fracture       |               |                 |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Plantar Fasciitis           |               |                 |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Spondylolisthesis           |               |                 |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Tendonitis                  |               |                 |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0               | 0             |
| Musculoskeletal Stiffness   |               |                 |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 15 (6.67%)  | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 2               | 0             |
| Infections and infestations |               |                 |               |

|                             |               |                |                |
|-----------------------------|---------------|----------------|----------------|
| Anal Abscess                |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 15 (6.67%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0             | 1              | 0              |
| Bronchitis                  |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Candidiasis                 |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 15 (6.67%) | 1 / 5 (20.00%) |
| occurrences (all)           | 0             | 1              | 1              |
| Cellulitis                  |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 15 (6.67%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0             | 1              | 0              |
| Cystitis                    |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Dacryocanaliculitis         |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Diarrhoea Infectious        |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Folliculitis                |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Fungal Infection            |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Fungal Skin Infection       |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Furuncle                    |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 15 (6.67%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0             | 2              | 0              |
| Gingival Infection          |               |                |                |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |

|                             |               |                |               |
|-----------------------------|---------------|----------------|---------------|
| Incision Site Infection     |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Influenza                   |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Kidney Infection            |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Lung Infection              |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Lymph Gland Infection       |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Nail Infection              |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Nasopharyngitis             |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Oral Candidiasis            |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Oral Herpes                 |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 15 (6.67%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 1              | 0             |
| Otitis Externa              |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Otitis Media                |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Paronychia                  |               |                |               |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 15 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| Pharyngitis                 |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Platelet Count Decreased    |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Pneumonia                   |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 2 / 15 (13.33%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 2               | 0              |
| Sepsis                      |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Sinusitis                   |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 1 / 5 (20.00%) |
| occurrences (all)           | 0              | 0               | 2              |
| Skin Infection              |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 2               | 0              |
| Staphylococcal Infection    |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Tinea Cruris                |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Tinea Pedis                 |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Tinea Versicolour           |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Tooth Abscess               |                |                 |                |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 1              | 0               | 0              |
| Tooth Infection             |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |

|                                                                                       |                      |                       |                     |
|---------------------------------------------------------------------------------------|----------------------|-----------------------|---------------------|
| Upper Respiratory Infection<br>subjects affected / exposed<br>occurrences (all)       | 0 / 3 (0.00%)<br>0   | 0 / 15 (0.00%)<br>0   | 1 / 5 (20.00%)<br>1 |
| Upper Respiratory Tract Infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0   | 0 / 15 (0.00%)<br>0   | 0 / 5 (0.00%)<br>0  |
| Urinary Tract Infection<br>subjects affected / exposed<br>occurrences (all)           | 0 / 3 (0.00%)<br>0   | 0 / 15 (0.00%)<br>0   | 3 / 5 (60.00%)<br>4 |
| Vaginal Infection<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 3 (0.00%)<br>0   | 0 / 15 (0.00%)<br>0   | 0 / 5 (0.00%)<br>0  |
| Viral Infection<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 3 (0.00%)<br>0   | 0 / 15 (0.00%)<br>0   | 0 / 5 (0.00%)<br>0  |
| Vulvovaginal Mycotic Infection<br>subjects affected / exposed<br>occurrences (all)    | 0 / 3 (0.00%)<br>0   | 0 / 15 (0.00%)<br>0   | 0 / 5 (0.00%)<br>0  |
| Wound Infection<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 3 (0.00%)<br>0   | 0 / 15 (0.00%)<br>0   | 0 / 5 (0.00%)<br>0  |
| Nasal Vestibulitis<br>subjects affected / exposed<br>occurrences (all)                | 0 / 3 (0.00%)<br>0   | 1 / 15 (6.67%)<br>1   | 0 / 5 (0.00%)<br>0  |
| Pneumonial Staphylococcal<br>subjects affected / exposed<br>occurrences (all)         | 0 / 3 (0.00%)<br>0   | 1 / 15 (6.67%)<br>1   | 0 / 5 (0.00%)<br>0  |
| Metabolism and nutrition disorders                                                    |                      |                       |                     |
| Cachexia<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 3 (0.00%)<br>0   | 0 / 15 (0.00%)<br>0   | 0 / 5 (0.00%)<br>0  |
| Decreased Appetite<br>subjects affected / exposed<br>occurrences (all)                | 3 / 3 (100.00%)<br>3 | 5 / 15 (33.33%)<br>10 | 3 / 5 (60.00%)<br>4 |
| Dehydration                                                                           |                      |                       |                     |

|                             |                 |                 |               |
|-----------------------------|-----------------|-----------------|---------------|
| subjects affected / exposed | 3 / 3 (100.00%) | 2 / 15 (13.33%) | 0 / 5 (0.00%) |
| occurrences (all)           | 5               | 3               | 0             |
| Glucose Tolerance Impaired  |                 |                 |               |
| subjects affected / exposed | 0 / 3 (0.00%)   | 0 / 15 (0.00%)  | 0 / 5 (0.00%) |
| occurrences (all)           | 0               | 0               | 0             |
| Hypercalcaemia              |                 |                 |               |
| subjects affected / exposed | 0 / 3 (0.00%)   | 1 / 15 (6.67%)  | 0 / 5 (0.00%) |
| occurrences (all)           | 0               | 1               | 0             |
| Hypercholesterolaemia       |                 |                 |               |
| subjects affected / exposed | 0 / 3 (0.00%)   | 2 / 15 (13.33%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0               | 2               | 0             |
| Hyperglycaemia              |                 |                 |               |
| subjects affected / exposed | 0 / 3 (0.00%)   | 1 / 15 (6.67%)  | 0 / 5 (0.00%) |
| occurrences (all)           | 0               | 2               | 0             |
| Hyperkalaemia               |                 |                 |               |
| subjects affected / exposed | 0 / 3 (0.00%)   | 2 / 15 (13.33%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0               | 4               | 0             |
| Hypernatraemia              |                 |                 |               |
| subjects affected / exposed | 0 / 3 (0.00%)   | 3 / 15 (20.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0               | 6               | 0             |
| Hyperuricaemia              |                 |                 |               |
| subjects affected / exposed | 0 / 3 (0.00%)   | 0 / 15 (0.00%)  | 0 / 5 (0.00%) |
| occurrences (all)           | 0               | 0               | 0             |
| Hypoalbuminaemia            |                 |                 |               |
| subjects affected / exposed | 1 / 3 (33.33%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%) |
| occurrences (all)           | 1               | 0               | 0             |
| Hypocalcaemia               |                 |                 |               |
| subjects affected / exposed | 0 / 3 (0.00%)   | 1 / 15 (6.67%)  | 0 / 5 (0.00%) |
| occurrences (all)           | 0               | 5               | 0             |
| Hypoglycaemia               |                 |                 |               |
| subjects affected / exposed | 0 / 3 (0.00%)   | 1 / 15 (6.67%)  | 0 / 5 (0.00%) |
| occurrences (all)           | 0               | 2               | 0             |
| Hypokalaemia                |                 |                 |               |
| subjects affected / exposed | 0 / 3 (0.00%)   | 1 / 15 (6.67%)  | 0 / 5 (0.00%) |
| occurrences (all)           | 0               | 3               | 0             |
| Hypomagnesaemia             |                 |                 |               |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 1 / 5 (20.00%) |
| occurrences (all)           | 0              | 2               | 1              |
| Hyponatraemia               |                |                 |                |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 15 (13.33%) | 1 / 5 (20.00%) |
| occurrences (all)           | 1              | 2               | 1              |
| Hypophosphataemia           |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 1 / 5 (20.00%) |
| occurrences (all)           | 0              | 1               | 2              |
| Hypoproteinaemia            |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Hypovolaemia                |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Type 2 Diabetes Mellitus    |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 0 / 15 (0.00%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Hyperphosphataemia          |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Hypertriglyceridaemia       |                |                 |                |
| subjects affected / exposed | 0 / 3 (0.00%)  | 1 / 15 (6.67%)  | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |

| <b>Non-serious adverse events</b>                                      | P2 Arm A: 5 mg<br>Axitinib BID | P2 Arm B: 10 mg/kg<br>TRC105 Wkly + 5<br>mg Axitinib BID |  |
|------------------------------------------------------------------------|--------------------------------|----------------------------------------------------------|--|
| Total subjects affected by non-serious<br>adverse events               |                                |                                                          |  |
| subjects affected / exposed                                            | 71 / 74 (95.95%)               | 72 / 73 (98.63%)                                         |  |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps) |                                |                                                          |  |
| Basal Cell Carcinoma                                                   |                                |                                                          |  |
| subjects affected / exposed                                            | 0 / 74 (0.00%)                 | 3 / 73 (4.11%)                                           |  |
| occurrences (all)                                                      | 0                              | 3                                                        |  |
| Benign Neoplasm                                                        |                                |                                                          |  |
| subjects affected / exposed                                            | 1 / 74 (1.35%)                 | 0 / 73 (0.00%)                                           |  |
| occurrences (all)                                                      | 1                              | 0                                                        |  |
| Breast Cancer                                                          |                                |                                                          |  |

|                             |                  |                  |  |
|-----------------------------|------------------|------------------|--|
| subjects affected / exposed | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |  |
| occurrences (all)           | 0                | 1                |  |
| Skin Papilloma              |                  |                  |  |
| subjects affected / exposed | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |  |
| occurrences (all)           | 1                | 0                |  |
| Vascular disorders          |                  |                  |  |
| Aortic Aneurysm             |                  |                  |  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |  |
| occurrences (all)           | 0                | 1                |  |
| Arteriosclerosis            |                  |                  |  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |  |
| occurrences (all)           | 0                | 1                |  |
| Deep Vein Thrombosis        |                  |                  |  |
| subjects affected / exposed | 2 / 74 (2.70%)   | 0 / 73 (0.00%)   |  |
| occurrences (all)           | 2                | 0                |  |
| Embolism                    |                  |                  |  |
| subjects affected / exposed | 1 / 74 (1.35%)   | 1 / 73 (1.37%)   |  |
| occurrences (all)           | 1                | 1                |  |
| Flushing                    |                  |                  |  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 7 / 73 (9.59%)   |  |
| occurrences (all)           | 0                | 8                |  |
| Haematoma                   |                  |                  |  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |  |
| occurrences (all)           | 0                | 1                |  |
| Haemorrhage                 |                  |                  |  |
| subjects affected / exposed | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |  |
| occurrences (all)           | 1                | 0                |  |
| Hot Flush                   |                  |                  |  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 2 / 73 (2.74%)   |  |
| occurrences (all)           | 0                | 4                |  |
| Hyperaemia                  |                  |                  |  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |  |
| occurrences (all)           | 0                | 1                |  |
| Hypertension                |                  |                  |  |
| subjects affected / exposed | 33 / 74 (44.59%) | 26 / 73 (35.62%) |  |
| occurrences (all)           | 61               | 47               |  |

|                                                                                                                         |                      |                      |  |
|-------------------------------------------------------------------------------------------------------------------------|----------------------|----------------------|--|
| Hypotension<br>subjects affected / exposed<br>occurrences (all)                                                         | 2 / 74 (2.70%)<br>2  | 7 / 73 (9.59%)<br>11 |  |
| Orthostatic Hypotension<br>subjects affected / exposed<br>occurrences (all)                                             | 1 / 74 (1.35%)<br>1  | 0 / 73 (0.00%)<br>0  |  |
| Thrombophlebitis Superficial<br>subjects affected / exposed<br>occurrences (all)                                        | 0 / 74 (0.00%)<br>0  | 1 / 73 (1.37%)<br>1  |  |
| Surgical and medical procedures<br>Colostomy<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 74 (0.00%)<br>0  | 1 / 73 (1.37%)<br>1  |  |
| Tooth Extraction<br>subjects affected / exposed<br>occurrences (all)                                                    | 0 / 74 (0.00%)<br>0  | 1 / 73 (1.37%)<br>2  |  |
| Preventive Surgery<br>subjects affected / exposed<br>occurrences (all)                                                  | 0 / 74 (0.00%)<br>0  | 0 / 73 (0.00%)<br>0  |  |
| General disorders and administration<br>site conditions<br>Asthenia<br>subjects affected / exposed<br>occurrences (all) | 9 / 74 (12.16%)<br>9 | 6 / 73 (8.22%)<br>8  |  |
| Catheter Site Pain<br>subjects affected / exposed<br>occurrences (all)                                                  | 0 / 74 (0.00%)<br>0  | 1 / 73 (1.37%)<br>1  |  |
| Catheter Site Swelling<br>subjects affected / exposed<br>occurrences (all)                                              | 0 / 74 (0.00%)<br>0  | 1 / 73 (1.37%)<br>1  |  |
| Chest Discomfort<br>subjects affected / exposed<br>occurrences (all)                                                    | 1 / 74 (1.35%)<br>1  | 0 / 73 (0.00%)<br>0  |  |
| Chest Pain<br>subjects affected / exposed<br>occurrences (all)                                                          | 4 / 74 (5.41%)<br>6  | 1 / 73 (1.37%)<br>1  |  |
| Chills                                                                                                                  |                      |                      |  |

|                                       |                  |                  |
|---------------------------------------|------------------|------------------|
| subjects affected / exposed           | 7 / 74 (9.46%)   | 11 / 73 (15.07%) |
| occurrences (all)                     | 9                | 13               |
| Drug Intolerance                      |                  |                  |
| subjects affected / exposed           | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |
| occurrences (all)                     | 1                | 0                |
| Facial Pain                           |                  |                  |
| subjects affected / exposed           | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)                     | 0                | 1                |
| Fatigue                               |                  |                  |
| subjects affected / exposed           | 40 / 74 (54.05%) | 42 / 73 (57.53%) |
| occurrences (all)                     | 75               | 72               |
| Feeling Cold                          |                  |                  |
| subjects affected / exposed           | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)                     | 0                | 1                |
| Feeling Hot                           |                  |                  |
| subjects affected / exposed           | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)                     | 0                | 1                |
| General Physical Health Deterioration |                  |                  |
| subjects affected / exposed           | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)                     | 0                | 1                |
| Influenza Like Illness                |                  |                  |
| subjects affected / exposed           | 3 / 74 (4.05%)   | 2 / 73 (2.74%)   |
| occurrences (all)                     | 3                | 3                |
| Infusion Site Erythema                |                  |                  |
| subjects affected / exposed           | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)                     | 0                | 1                |
| Infusion Site Extravasation           |                  |                  |
| subjects affected / exposed           | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)                     | 0                | 1                |
| Injection Site Erythema               |                  |                  |
| subjects affected / exposed           | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)                     | 0                | 1                |
| Injection Site Haemorrhage            |                  |                  |
| subjects affected / exposed           | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)                     | 0                | 1                |
| Injection Site Mass                   |                  |                  |

|                             |                |                  |
|-----------------------------|----------------|------------------|
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%)   |
| occurrences (all)           | 1              | 0                |
| Local Swelling              |                |                  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%)   |
| occurrences (all)           | 1              | 0                |
| Malaise                     |                |                  |
| subjects affected / exposed | 4 / 74 (5.41%) | 3 / 73 (4.11%)   |
| occurrences (all)           | 4              | 3                |
| Medical Device Site Bruise  |                |                  |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%)   |
| occurrences (all)           | 0              | 1                |
| Mucosal Inflammation        |                |                  |
| subjects affected / exposed | 6 / 74 (8.11%) | 10 / 73 (13.70%) |
| occurrences (all)           | 9              | 11               |
| Non-Cardiac Chest Pain      |                |                  |
| subjects affected / exposed | 4 / 74 (5.41%) | 3 / 73 (4.11%)   |
| occurrences (all)           | 5              | 4                |
| Oedema                      |                |                  |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%)   |
| occurrences (all)           | 0              | 2                |
| Oedema Peripheral           |                |                  |
| subjects affected / exposed | 5 / 74 (6.76%) | 5 / 73 (6.85%)   |
| occurrences (all)           | 12             | 6                |
| Pain                        |                |                  |
| subjects affected / exposed | 2 / 74 (2.70%) | 2 / 73 (2.74%)   |
| occurrences (all)           | 2              | 2                |
| Pyrexia                     |                |                  |
| subjects affected / exposed | 4 / 74 (5.41%) | 10 / 73 (13.70%) |
| occurrences (all)           | 4              | 10               |
| Temperature Intolerance     |                |                  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%)   |
| occurrences (all)           | 1              | 0                |
| Thirst                      |                |                  |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%)   |
| occurrences (all)           | 0              | 1                |
| Gait Disturbance            |                |                  |

|                                                  |                     |                     |  |
|--------------------------------------------------|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 74 (0.00%)<br>0 | 0 / 73 (0.00%)<br>0 |  |
| Immune system disorders                          |                     |                     |  |
| Hypersensitivity                                 |                     |                     |  |
| subjects affected / exposed                      | 1 / 74 (1.35%)      | 1 / 73 (1.37%)      |  |
| occurrences (all)                                | 1                   | 1                   |  |
| Seasonal Allergy                                 |                     |                     |  |
| subjects affected / exposed                      | 1 / 74 (1.35%)      | 0 / 73 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Reproductive system and breast disorders         |                     |                     |  |
| Breast Pain                                      |                     |                     |  |
| subjects affected / exposed                      | 0 / 74 (0.00%)      | 2 / 73 (2.74%)      |  |
| occurrences (all)                                | 0                   | 2                   |  |
| Erectile Dysfunction                             |                     |                     |  |
| subjects affected / exposed                      | 0 / 74 (0.00%)      | 1 / 73 (1.37%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Genital Discharge                                |                     |                     |  |
| subjects affected / exposed                      | 1 / 74 (1.35%)      | 0 / 73 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Gynaecomastia                                    |                     |                     |  |
| subjects affected / exposed                      | 1 / 74 (1.35%)      | 0 / 73 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Nipple Pain                                      |                     |                     |  |
| subjects affected / exposed                      | 0 / 74 (0.00%)      | 1 / 73 (1.37%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Pelvic Pain                                      |                     |                     |  |
| subjects affected / exposed                      | 0 / 74 (0.00%)      | 2 / 73 (2.74%)      |  |
| occurrences (all)                                | 0                   | 2                   |  |
| Prostatic Obstruction                            |                     |                     |  |
| subjects affected / exposed                      | 1 / 74 (1.35%)      | 0 / 73 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Scrotal Pain                                     |                     |                     |  |
| subjects affected / exposed                      | 0 / 74 (0.00%)      | 1 / 73 (1.37%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Vaginal Lesion                                   |                     |                     |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |  |
| occurrences (all)                               | 0                | 1                |  |
| Vulvovaginal Pain                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |  |
| occurrences (all)                               | 0                | 1                |  |
| Respiratory, thoracic and mediastinal disorders |                  |                  |  |
| Choking Sensation                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |  |
| occurrences (all)                               | 0                | 1                |  |
| Cough                                           |                  |                  |  |
| subjects affected / exposed                     | 15 / 74 (20.27%) | 14 / 73 (19.18%) |  |
| occurrences (all)                               | 24               | 18               |  |
| Dry Throat                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |  |
| occurrences (all)                               | 0                | 1                |  |
| Dysphonia                                       |                  |                  |  |
| subjects affected / exposed                     | 27 / 74 (36.49%) | 19 / 73 (26.03%) |  |
| occurrences (all)                               | 34               | 21               |  |
| Dyspnoea                                        |                  |                  |  |
| subjects affected / exposed                     | 10 / 74 (13.51%) | 12 / 73 (16.44%) |  |
| occurrences (all)                               | 18               | 15               |  |
| Dyspnoea Exertional                             |                  |                  |  |
| subjects affected / exposed                     | 3 / 74 (4.05%)   | 3 / 73 (4.11%)   |  |
| occurrences (all)                               | 4                | 3                |  |
| Epistaxis                                       |                  |                  |  |
| subjects affected / exposed                     | 5 / 74 (6.76%)   | 47 / 73 (64.38%) |  |
| occurrences (all)                               | 6                | 68               |  |
| Haemoptysis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 74 (0.00%)   | 2 / 73 (2.74%)   |  |
| occurrences (all)                               | 0                | 2                |  |
| Hiccups                                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |  |
| occurrences (all)                               | 1                | 0                |  |
| Hypoxia                                         |                  |                  |  |

|                                  |                |                  |
|----------------------------------|----------------|------------------|
| subjects affected / exposed      | 1 / 74 (1.35%) | 3 / 73 (4.11%)   |
| occurrences (all)                | 1              | 6                |
| Increased Upper Airway Secretion |                |                  |
| subjects affected / exposed      | 1 / 74 (1.35%) | 0 / 73 (0.00%)   |
| occurrences (all)                | 1              | 0                |
| Nasal Congestion                 |                |                  |
| subjects affected / exposed      | 4 / 74 (5.41%) | 6 / 73 (8.22%)   |
| occurrences (all)                | 5              | 6                |
| Nasal Dryness                    |                |                  |
| subjects affected / exposed      | 0 / 74 (0.00%) | 2 / 73 (2.74%)   |
| occurrences (all)                | 0              | 2                |
| Nasal Septum Disorder            |                |                  |
| subjects affected / exposed      | 0 / 74 (0.00%) | 1 / 73 (1.37%)   |
| occurrences (all)                | 0              | 1                |
| Nasal Septum Perforation         |                |                  |
| subjects affected / exposed      | 0 / 74 (0.00%) | 1 / 73 (1.37%)   |
| occurrences (all)                | 0              | 1                |
| Nasal Septum Ulceration          |                |                  |
| subjects affected / exposed      | 0 / 74 (0.00%) | 1 / 73 (1.37%)   |
| occurrences (all)                | 0              | 1                |
| Nasal Ulcer                      |                |                  |
| subjects affected / exposed      | 0 / 74 (0.00%) | 1 / 73 (1.37%)   |
| occurrences (all)                | 0              | 1                |
| Oropharyngeal Pain               |                |                  |
| subjects affected / exposed      | 6 / 74 (8.11%) | 13 / 73 (17.81%) |
| occurrences (all)                | 7              | 14               |
| Pleural Effusion                 |                |                  |
| subjects affected / exposed      | 0 / 74 (0.00%) | 2 / 73 (2.74%)   |
| occurrences (all)                | 0              | 3                |
| Productive Cough                 |                |                  |
| subjects affected / exposed      | 3 / 74 (4.05%) | 4 / 73 (5.48%)   |
| occurrences (all)                | 3              | 6                |
| Pulmonary Embolism               |                |                  |
| subjects affected / exposed      | 1 / 74 (1.35%) | 0 / 73 (0.00%)   |
| occurrences (all)                | 1              | 0                |
| Respiratory Tract Congestion     |                |                  |

|                                      |                |                |  |
|--------------------------------------|----------------|----------------|--|
| subjects affected / exposed          | 1 / 74 (1.35%) | 1 / 73 (1.37%) |  |
| occurrences (all)                    | 1              | 1              |  |
| Rhinitis Allergic                    |                |                |  |
| subjects affected / exposed          | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences (all)                    | 0              | 1              |  |
| Rhinorrhoea                          |                |                |  |
| subjects affected / exposed          | 2 / 74 (2.70%) | 5 / 73 (6.85%) |  |
| occurrences (all)                    | 2              | 5              |  |
| Sinus Congestion                     |                |                |  |
| subjects affected / exposed          | 2 / 74 (2.70%) | 2 / 73 (2.74%) |  |
| occurrences (all)                    | 2              | 2              |  |
| Sleep Apnoea Syndrome                |                |                |  |
| subjects affected / exposed          | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences (all)                    | 0              | 2              |  |
| Tachypnoea                           |                |                |  |
| subjects affected / exposed          | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences (all)                    | 1              | 0              |  |
| Upper Respiratory Tract Inflammation |                |                |  |
| subjects affected / exposed          | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences (all)                    | 1              | 0              |  |
| Upper-airway Cough Syndrome          |                |                |  |
| subjects affected / exposed          | 1 / 74 (1.35%) | 3 / 73 (4.11%) |  |
| occurrences (all)                    | 1              | 3              |  |
| Wheezing                             |                |                |  |
| subjects affected / exposed          | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences (all)                    | 2              | 0              |  |
| Psychiatric disorders                |                |                |  |
| Agitation                            |                |                |  |
| subjects affected / exposed          | 1 / 74 (1.35%) | 2 / 73 (2.74%) |  |
| occurrences (all)                    | 1              | 2              |  |
| Anxiety                              |                |                |  |
| subjects affected / exposed          | 5 / 74 (6.76%) | 2 / 73 (2.74%) |  |
| occurrences (all)                    | 6              | 2              |  |
| Confusional State                    |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 74 (1.35%) | 4 / 73 (5.48%) |  |
| occurrences (all)                               | 1              | 5              |  |
| Delirium                                        |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 1 / 73 (1.37%) |  |
| occurrences (all)                               | 1              | 2              |  |
| Depression                                      |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences (all)                               | 1              | 0              |  |
| Insomnia                                        |                |                |  |
| subjects affected / exposed                     | 6 / 74 (8.11%) | 5 / 73 (6.85%) |  |
| occurrences (all)                               | 7              | 5              |  |
| Mental Status Changes                           |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Investigations                                  |                |                |  |
| Activated Partial Thromboplastin Time Prolonged |                |                |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 2 / 73 (2.74%) |  |
| occurrences (all)                               | 0              | 2              |  |
| Alanine Aminotransferase Increased              |                |                |  |
| subjects affected / exposed                     | 4 / 74 (5.41%) | 4 / 73 (5.48%) |  |
| occurrences (all)                               | 4              | 7              |  |
| Aspartate Aminotransferase Increased            |                |                |  |
| subjects affected / exposed                     | 7 / 74 (9.46%) | 5 / 73 (6.85%) |  |
| occurrences (all)                               | 9              | 7              |  |
| Blood Alkaline Phosphatase Increased            |                |                |  |
| subjects affected / exposed                     | 2 / 74 (2.70%) | 7 / 73 (9.59%) |  |
| occurrences (all)                               | 2              | 7              |  |
| Blood Amylase Increased                         |                |                |  |
| subjects affected / exposed                     | 7 / 74 (9.46%) | 2 / 73 (2.74%) |  |
| occurrences (all)                               | 15             | 7              |  |
| Blood Bilirubin Increased                       |                |                |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 1 / 73 (1.37%) |  |
| occurrences (all)                               | 1              | 1              |  |
| Blood Creatinine Increased                      |                |                |  |

|                                             |                 |                |
|---------------------------------------------|-----------------|----------------|
| subjects affected / exposed                 | 9 / 74 (12.16%) | 5 / 73 (6.85%) |
| occurrences (all)                           | 14              | 9              |
| Blood Pressure Increased                    |                 |                |
| subjects affected / exposed                 | 2 / 74 (2.70%)  | 1 / 73 (1.37%) |
| occurrences (all)                           | 4               | 5              |
| Blood Thyroid Stimulating Hormone Decreased |                 |                |
| subjects affected / exposed                 | 1 / 74 (1.35%)  | 0 / 73 (0.00%) |
| occurrences (all)                           | 1               | 0              |
| Blood Thyroid Stimulating Hormone Increased |                 |                |
| subjects affected / exposed                 | 4 / 74 (5.41%)  | 5 / 73 (6.85%) |
| occurrences (all)                           | 6               | 8              |
| Blood Urea Increased                        |                 |                |
| subjects affected / exposed                 | 2 / 74 (2.70%)  | 0 / 73 (0.00%) |
| occurrences (all)                           | 2               | 0              |
| Cardiac Murmur                              |                 |                |
| subjects affected / exposed                 | 0 / 74 (0.00%)  | 1 / 73 (1.37%) |
| occurrences (all)                           | 0               | 1              |
| Electrocardiogram QT Prolonged              |                 |                |
| subjects affected / exposed                 | 0 / 74 (0.00%)  | 3 / 73 (4.11%) |
| occurrences (all)                           | 0               | 3              |
| Epidermal Growth Factor Receptor Increased  |                 |                |
| subjects affected / exposed                 | 1 / 74 (1.35%)  | 0 / 73 (0.00%) |
| occurrences (all)                           | 1               | 0              |
| Gamma-Glutamyltransferase Increased         |                 |                |
| subjects affected / exposed                 | 0 / 74 (0.00%)  | 2 / 73 (2.74%) |
| occurrences (all)                           | 0               | 7              |
| Glucose Urine Present                       |                 |                |
| subjects affected / exposed                 | 0 / 74 (0.00%)  | 1 / 73 (1.37%) |
| occurrences (all)                           | 0               | 1              |
| Haemoglobin Increased                       |                 |                |
| subjects affected / exposed                 | 1 / 74 (1.35%)  | 0 / 73 (0.00%) |
| occurrences (all)                           | 1               | 0              |
| International Normalised Ratio Increased    |                 |                |

|                                                  |                  |                  |
|--------------------------------------------------|------------------|------------------|
| subjects affected / exposed                      | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)                                | 0                | 1                |
| Iron Binding Capacity Total Decreased            |                  |                  |
| subjects affected / exposed                      | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |
| occurrences (all)                                | 1                | 0                |
| Lipase Increased                                 |                  |                  |
| subjects affected / exposed                      | 5 / 74 (6.76%)   | 2 / 73 (2.74%)   |
| occurrences (all)                                | 5                | 3                |
| Liver Function Test Abnormal                     |                  |                  |
| subjects affected / exposed                      | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |
| occurrences (all)                                | 2                | 0                |
| Liver Function Test Increased                    |                  |                  |
| subjects affected / exposed                      | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |
| occurrences (all)                                | 1                | 0                |
| Lymphocyte Count Decreased                       |                  |                  |
| subjects affected / exposed                      | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)                                | 0                | 1                |
| Mycobacterium Tuberculosis Complex Test Positive |                  |                  |
| subjects affected / exposed                      | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)                                | 0                | 1                |
| Red Blood Cells Urine                            |                  |                  |
| subjects affected / exposed                      | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |
| occurrences (all)                                | 1                | 0                |
| Transaminases Increased                          |                  |                  |
| subjects affected / exposed                      | 2 / 74 (2.70%)   | 0 / 73 (0.00%)   |
| occurrences (all)                                | 3                | 0                |
| Vitamin D Decreased                              |                  |                  |
| subjects affected / exposed                      | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)                                | 0                | 1                |
| Weight Decreased                                 |                  |                  |
| subjects affected / exposed                      | 17 / 74 (22.97%) | 27 / 73 (36.99%) |
| occurrences (all)                                | 41               | 68               |
| Weight Increased                                 |                  |                  |

|                                                |                |                  |  |
|------------------------------------------------|----------------|------------------|--|
| subjects affected / exposed                    | 1 / 74 (1.35%) | 0 / 73 (0.00%)   |  |
| occurrences (all)                              | 1              | 0                |  |
| White Blood Cell Count Decreased               |                |                  |  |
| subjects affected / exposed                    | 1 / 74 (1.35%) | 0 / 73 (0.00%)   |  |
| occurrences (all)                              | 1              | 0                |  |
| White Blood Cells Urine                        |                |                  |  |
| subjects affected / exposed                    | 1 / 74 (1.35%) | 0 / 73 (0.00%)   |  |
| occurrences (all)                              | 1              | 0                |  |
| Food Intolerance                               |                |                  |  |
| subjects affected / exposed                    | 1 / 74 (1.35%) | 0 / 73 (0.00%)   |  |
| occurrences (all)                              | 1              | 0                |  |
| Gout                                           |                |                  |  |
| subjects affected / exposed                    | 2 / 74 (2.70%) | 1 / 73 (1.37%)   |  |
| occurrences (all)                              | 2              | 1                |  |
| Injury, poisoning and procedural complications |                |                  |  |
| Contusion                                      |                |                  |  |
| subjects affected / exposed                    | 1 / 74 (1.35%) | 1 / 73 (1.37%)   |  |
| occurrences (all)                              | 1              | 1                |  |
| Fall                                           |                |                  |  |
| subjects affected / exposed                    | 3 / 74 (4.05%) | 4 / 73 (5.48%)   |  |
| occurrences (all)                              | 4              | 5                |  |
| Head Injury                                    |                |                  |  |
| subjects affected / exposed                    | 1 / 74 (1.35%) | 0 / 73 (0.00%)   |  |
| occurrences (all)                              | 1              | 0                |  |
| Incisional Hernia                              |                |                  |  |
| subjects affected / exposed                    | 1 / 74 (1.35%) | 0 / 73 (0.00%)   |  |
| occurrences (all)                              | 1              | 0                |  |
| Infusion Related Reaction                      |                |                  |  |
| subjects affected / exposed                    | 0 / 74 (0.00%) | 19 / 73 (26.03%) |  |
| occurrences (all)                              | 0              | 21               |  |
| Joint Injury                                   |                |                  |  |
| subjects affected / exposed                    | 1 / 74 (1.35%) | 0 / 73 (0.00%)   |  |
| occurrences (all)                              | 1              | 0                |  |
| Laceration                                     |                |                  |  |

|                             |                |                |
|-----------------------------|----------------|----------------|
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Limb Injury                 |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Lower Limb Fracture         |                |                |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%) |
| occurrences (all)           | 0              | 2              |
| Muscle Strain               |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Post Procedural Discomfort  |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Procedural pain             |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Rib Fracture                |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Road Traffic Accident       |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Skin Abrasion               |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Sternal Fracture            |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Thermal Burn                |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Wound                       |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Wound Complication          |                |                |

|                             |                |                |  |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |
| Wound Dehiscence            |                |                |  |
| subjects affected / exposed | 0 / 74 (0.00%) | 2 / 73 (2.74%) |  |
| occurrences (all)           | 0              | 2              |  |
| Cardiac disorders           |                |                |  |
| Acute Coronary Syndrome     |                |                |  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |
| Angina Pectoris             |                |                |  |
| subjects affected / exposed | 1 / 74 (1.35%) | 1 / 73 (1.37%) |  |
| occurrences (all)           | 1              | 1              |  |
| Arrhythmia                  |                |                |  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |
| Bradycardia                 |                |                |  |
| subjects affected / exposed | 3 / 74 (4.05%) | 0 / 73 (0.00%) |  |
| occurrences (all)           | 3              | 0              |  |
| Bundle Branch Block Right   |                |                |  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |
| Cardiac Disorder            |                |                |  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |
| Cardiac Failure             |                |                |  |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences (all)           | 0              | 1              |  |
| Cardiac Failure Acute       |                |                |  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |
| Coronary Artery Disease     |                |                |  |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences (all)           | 0              | 1              |  |
| Coronary Artery Thrombosis  |                |                |  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |

|                                |                |                |
|--------------------------------|----------------|----------------|
| Diastolic Dysfunction          |                |                |
| subjects affected / exposed    | 0 / 74 (0.00%) | 1 / 73 (1.37%) |
| occurrences (all)              | 0              | 1              |
| Left Ventricular Dysfunction   |                |                |
| subjects affected / exposed    | 0 / 74 (0.00%) | 1 / 73 (1.37%) |
| occurrences (all)              | 0              | 1              |
| Mitral Valve Incompetence      |                |                |
| subjects affected / exposed    | 0 / 74 (0.00%) | 1 / 73 (1.37%) |
| occurrences (all)              | 0              | 1              |
| Pericardial Effusion           |                |                |
| subjects affected / exposed    | 1 / 74 (1.35%) | 2 / 73 (2.74%) |
| occurrences (all)              | 1              | 2              |
| Sinus Bradycardia              |                |                |
| subjects affected / exposed    | 1 / 74 (1.35%) | 2 / 73 (2.74%) |
| occurrences (all)              | 1              | 2              |
| Sinus Tachycardia              |                |                |
| subjects affected / exposed    | 2 / 74 (2.70%) | 1 / 73 (1.37%) |
| occurrences (all)              | 2              | 1              |
| Supraventricular Extrasystoles |                |                |
| subjects affected / exposed    | 1 / 74 (1.35%) | 1 / 73 (1.37%) |
| occurrences (all)              | 1              | 1              |
| Tachycardia                    |                |                |
| subjects affected / exposed    | 1 / 74 (1.35%) | 5 / 73 (6.85%) |
| occurrences (all)              | 1              | 6              |
| Tricuspid Valve Incompetence   |                |                |
| subjects affected / exposed    | 0 / 74 (0.00%) | 1 / 73 (1.37%) |
| occurrences (all)              | 0              | 1              |
| Ventricular Extrasystoles      |                |                |
| subjects affected / exposed    | 0 / 74 (0.00%) | 3 / 73 (4.11%) |
| occurrences (all)              | 0              | 3              |
| Wandering Pacemaker            |                |                |
| subjects affected / exposed    | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)              | 1              | 0              |
| Palpitations                   |                |                |
| subjects affected / exposed    | 0 / 74 (0.00%) | 0 / 73 (0.00%) |
| occurrences (all)              | 0              | 0              |

|                             |                 |                  |  |
|-----------------------------|-----------------|------------------|--|
| Nervous system disorders    |                 |                  |  |
| Amnesia                     |                 |                  |  |
| subjects affected / exposed | 2 / 74 (2.70%)  | 0 / 73 (0.00%)   |  |
| occurrences (all)           | 2               | 0                |  |
| Balance Disorder            |                 |                  |  |
| subjects affected / exposed | 0 / 74 (0.00%)  | 2 / 73 (2.74%)   |  |
| occurrences (all)           | 0               | 2                |  |
| Burning Sensation           |                 |                  |  |
| subjects affected / exposed | 0 / 74 (0.00%)  | 1 / 73 (1.37%)   |  |
| occurrences (all)           | 0               | 1                |  |
| Cerebrovascular Accident    |                 |                  |  |
| subjects affected / exposed | 0 / 74 (0.00%)  | 1 / 73 (1.37%)   |  |
| occurrences (all)           | 0               | 1                |  |
| Cognitive Disorder          |                 |                  |  |
| subjects affected / exposed | 0 / 74 (0.00%)  | 1 / 73 (1.37%)   |  |
| occurrences (all)           | 0               | 1                |  |
| Convulsion                  |                 |                  |  |
| subjects affected / exposed | 0 / 74 (0.00%)  | 1 / 73 (1.37%)   |  |
| occurrences (all)           | 0               | 1                |  |
| Disturbance In Attention    |                 |                  |  |
| subjects affected / exposed | 0 / 74 (0.00%)  | 1 / 73 (1.37%)   |  |
| occurrences (all)           | 0               | 1                |  |
| Dizziness                   |                 |                  |  |
| subjects affected / exposed | 9 / 74 (12.16%) | 10 / 73 (13.70%) |  |
| occurrences (all)           | 10              | 11               |  |
| Dizziness Postural          |                 |                  |  |
| subjects affected / exposed | 2 / 74 (2.70%)  | 0 / 73 (0.00%)   |  |
| occurrences (all)           | 2               | 0                |  |
| Dysaesthesia                |                 |                  |  |
| subjects affected / exposed | 0 / 74 (0.00%)  | 1 / 73 (1.37%)   |  |
| occurrences (all)           | 0               | 4                |  |
| Dysgeusia                   |                 |                  |  |
| subjects affected / exposed | 9 / 74 (12.16%) | 10 / 73 (13.70%) |  |
| occurrences (all)           | 9               | 12               |  |
| Dyskinesia                  |                 |                  |  |

|                             |                  |                  |
|-----------------------------|------------------|------------------|
| subjects affected / exposed | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)           | 0                | 1                |
| Encephalopathy              |                  |                  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)           | 0                | 1                |
| Headache                    |                  |                  |
| subjects affected / exposed | 12 / 74 (16.22%) | 47 / 73 (64.38%) |
| occurrences (all)           | 18               | 88               |
| Hyperaesthesia              |                  |                  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)           | 0                | 1                |
| Hypersomnia                 |                  |                  |
| subjects affected / exposed | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |
| occurrences (all)           | 1                | 0                |
| Hypoaesthesia               |                  |                  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)           | 0                | 1                |
| Hypotonia                   |                  |                  |
| subjects affected / exposed | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |
| occurrences (all)           | 1                | 0                |
| Lethargy                    |                  |                  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)           | 0                | 1                |
| Memory Impairment           |                  |                  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 2 / 73 (2.74%)   |
| occurrences (all)           | 0                | 3                |
| Mental Impairment           |                  |                  |
| subjects affected / exposed | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |
| occurrences (all)           | 1                | 0                |
| Metabolic Encephalopathy    |                  |                  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)           | 0                | 1                |
| Migraine                    |                  |                  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 5 / 73 (6.85%)   |
| occurrences (all)           | 0                | 8                |
| Neuropathy Peripheral       |                  |                  |

|                               |                |                |
|-------------------------------|----------------|----------------|
| subjects affected / exposed   | 2 / 74 (2.70%) | 0 / 73 (0.00%) |
| occurrences (all)             | 2              | 0              |
| Paraesthesia                  |                |                |
| subjects affected / exposed   | 3 / 74 (4.05%) | 2 / 73 (2.74%) |
| occurrences (all)             | 3              | 2              |
| Paresis                       |                |                |
| subjects affected / exposed   | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)             | 1              | 0              |
| Peripheral Sensory Neuropathy |                |                |
| subjects affected / exposed   | 2 / 74 (2.70%) | 1 / 73 (1.37%) |
| occurrences (all)             | 2              | 2              |
| Presyncope                    |                |                |
| subjects affected / exposed   | 1 / 74 (1.35%) | 2 / 73 (2.74%) |
| occurrences (all)             | 1              | 2              |
| Sciatica                      |                |                |
| subjects affected / exposed   | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)             | 1              | 0              |
| Sinus Headache                |                |                |
| subjects affected / exposed   | 0 / 74 (0.00%) | 1 / 73 (1.37%) |
| occurrences (all)             | 0              | 2              |
| Spinal Cord Compression       |                |                |
| subjects affected / exposed   | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)             | 1              | 0              |
| Syncope                       |                |                |
| subjects affected / exposed   | 2 / 74 (2.70%) | 3 / 73 (4.11%) |
| occurrences (all)             | 2              | 3              |
| Tremor                        |                |                |
| subjects affected / exposed   | 3 / 74 (4.05%) | 1 / 73 (1.37%) |
| occurrences (all)             | 3              | 1              |
| Somnolence                    |                |                |
| subjects affected / exposed   | 0 / 74 (0.00%) | 0 / 73 (0.00%) |
| occurrences (all)             | 0              | 0              |
| Speech Disorder               |                |                |
| subjects affected / exposed   | 0 / 74 (0.00%) | 0 / 73 (0.00%) |
| occurrences (all)             | 0              | 0              |
| Ageusia                       |                |                |

|                                                  |                     |                     |  |
|--------------------------------------------------|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 74 (0.00%)<br>0 | 0 / 73 (0.00%)<br>0 |  |
| Blood and lymphatic system disorders             |                     |                     |  |
| Anaemia                                          |                     |                     |  |
| subjects affected / exposed                      | 12 / 74 (16.22%)    | 16 / 73 (21.92%)    |  |
| occurrences (all)                                | 16                  | 69                  |  |
| Leukocytosis                                     |                     |                     |  |
| subjects affected / exposed                      | 0 / 74 (0.00%)      | 2 / 73 (2.74%)      |  |
| occurrences (all)                                | 0                   | 4                   |  |
| Leukopenia                                       |                     |                     |  |
| subjects affected / exposed                      | 0 / 74 (0.00%)      | 1 / 73 (1.37%)      |  |
| occurrences (all)                                | 0                   | 3                   |  |
| Microcytic Anaemia                               |                     |                     |  |
| subjects affected / exposed                      | 0 / 74 (0.00%)      | 1 / 73 (1.37%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Neutropenia                                      |                     |                     |  |
| subjects affected / exposed                      | 1 / 74 (1.35%)      | 1 / 73 (1.37%)      |  |
| occurrences (all)                                | 3                   | 2                   |  |
| Polycythaemia                                    |                     |                     |  |
| subjects affected / exposed                      | 2 / 74 (2.70%)      | 1 / 73 (1.37%)      |  |
| occurrences (all)                                | 3                   | 1                   |  |
| Thrombocytosis                                   |                     |                     |  |
| subjects affected / exposed                      | 0 / 74 (0.00%)      | 3 / 73 (4.11%)      |  |
| occurrences (all)                                | 0                   | 4                   |  |
| Haemolytic Anaemia                               |                     |                     |  |
| subjects affected / exposed                      | 0 / 74 (0.00%)      | 0 / 73 (0.00%)      |  |
| occurrences (all)                                | 0                   | 0                   |  |
| Ear and labyrinth disorders                      |                     |                     |  |
| Cerumen Impaction                                |                     |                     |  |
| subjects affected / exposed                      | 0 / 74 (0.00%)      | 1 / 73 (1.37%)      |  |
| occurrences (all)                                | 0                   | 2                   |  |
| Ear Discomfort                                   |                     |                     |  |
| subjects affected / exposed                      | 1 / 74 (1.35%)      | 0 / 73 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Ear Pain                                         |                     |                     |  |

|                               |                |                |  |
|-------------------------------|----------------|----------------|--|
| subjects affected / exposed   | 2 / 74 (2.70%) | 3 / 73 (4.11%) |  |
| occurrences (all)             | 2              | 3              |  |
| Hearing Impaired              |                |                |  |
| subjects affected / exposed   | 2 / 74 (2.70%) | 2 / 73 (2.74%) |  |
| occurrences (all)             | 2              | 2              |  |
| Hypoacusis                    |                |                |  |
| subjects affected / exposed   | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences (all)             | 1              | 0              |  |
| Tinnitus                      |                |                |  |
| subjects affected / exposed   | 1 / 74 (1.35%) | 3 / 73 (4.11%) |  |
| occurrences (all)             | 1              | 3              |  |
| Tympanic Membrane Perforation |                |                |  |
| subjects affected / exposed   | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences (all)             | 0              | 1              |  |
| Vertigo                       |                |                |  |
| subjects affected / exposed   | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences (all)             | 0              | 1              |  |
| Ear Haemorrhage               |                |                |  |
| subjects affected / exposed   | 0 / 74 (0.00%) | 0 / 73 (0.00%) |  |
| occurrences (all)             | 0              | 0              |  |
| Eye disorders                 |                |                |  |
| Cataract                      |                |                |  |
| subjects affected / exposed   | 2 / 74 (2.70%) | 0 / 73 (0.00%) |  |
| occurrences (all)             | 2              | 0              |  |
| Eye Discharge                 |                |                |  |
| subjects affected / exposed   | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences (all)             | 0              | 1              |  |
| Eye Pain                      |                |                |  |
| subjects affected / exposed   | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences (all)             | 1              | 0              |  |
| Lacrimation increased         |                |                |  |
| subjects affected / exposed   | 0 / 74 (0.00%) | 2 / 73 (2.74%) |  |
| occurrences (all)             | 0              | 2              |  |
| Periorbital Oedema            |                |                |  |
| subjects affected / exposed   | 0 / 74 (0.00%) | 2 / 73 (2.74%) |  |
| occurrences (all)             | 0              | 2              |  |

|                             |                |                  |  |
|-----------------------------|----------------|------------------|--|
| Photophobia                 |                |                  |  |
| subjects affected / exposed | 1 / 74 (1.35%) | 2 / 73 (2.74%)   |  |
| occurrences (all)           | 1              | 2                |  |
| Retinal Vein Occlusion      |                |                  |  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%)   |  |
| occurrences (all)           | 1              | 0                |  |
| Vision Blurred              |                |                  |  |
| subjects affected / exposed | 4 / 74 (5.41%) | 2 / 73 (2.74%)   |  |
| occurrences (all)           | 4              | 2                |  |
| Visual Impairment           |                |                  |  |
| subjects affected / exposed | 0 / 74 (0.00%) | 2 / 73 (2.74%)   |  |
| occurrences (all)           | 0              | 2                |  |
| Ocular Hyperaemia           |                |                  |  |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 73 (0.00%)   |  |
| occurrences (all)           | 0              | 0                |  |
| Gastrointestinal disorders  |                |                  |  |
| Abdominal Discomfort        |                |                  |  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%)   |  |
| occurrences (all)           | 1              | 0                |  |
| Abdominal Distension        |                |                  |  |
| subjects affected / exposed | 3 / 74 (4.05%) | 1 / 73 (1.37%)   |  |
| occurrences (all)           | 4              | 1                |  |
| Abdominal Hernia            |                |                  |  |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%)   |  |
| occurrences (all)           | 0              | 1                |  |
| Abdominal Pain              |                |                  |  |
| subjects affected / exposed | 2 / 74 (2.70%) | 10 / 73 (13.70%) |  |
| occurrences (all)           | 16             | 11               |  |
| Abdominal Pain Lower        |                |                  |  |
| subjects affected / exposed | 1 / 74 (1.35%) | 2 / 73 (2.74%)   |  |
| occurrences (all)           | 4              | 2                |  |
| Abdominal Pain Upper        |                |                  |  |
| subjects affected / exposed | 5 / 74 (6.76%) | 11 / 73 (15.07%) |  |
| occurrences (all)           | 6              | 18               |  |
| Abdominal Tenderness        |                |                  |  |

|                             |                  |                  |
|-----------------------------|------------------|------------------|
| subjects affected / exposed | 1 / 74 (1.35%)   | 1 / 73 (1.37%)   |
| occurrences (all)           | 1                | 1                |
| Anorectal Discomfort        |                  |                  |
| subjects affected / exposed | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |
| occurrences (all)           | 1                | 0                |
| Ascites                     |                  |                  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)           | 0                | 1                |
| Cheilitis                   |                  |                  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)           | 0                | 2                |
| Colitis                     |                  |                  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)           | 0                | 1                |
| Constipation                |                  |                  |
| subjects affected / exposed | 13 / 74 (17.57%) | 21 / 73 (28.77%) |
| occurrences (all)           | 16               | 26               |
| Dental Caries               |                  |                  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 3 / 73 (4.11%)   |
| occurrences (all)           | 0                | 3                |
| Diarrhoea                   |                  |                  |
| subjects affected / exposed | 46 / 74 (62.16%) | 42 / 73 (57.53%) |
| occurrences (all)           | 120              | 139              |
| Diverticulum                |                  |                  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)           | 0                | 1                |
| Dry Mouth                   |                  |                  |
| subjects affected / exposed | 7 / 74 (9.46%)   | 7 / 73 (9.59%)   |
| occurrences (all)           | 7                | 7                |
| Dyskinesia Oesophageal      |                  |                  |
| subjects affected / exposed | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |
| occurrences (all)           | 2                | 0                |
| Dyspepsia                   |                  |                  |
| subjects affected / exposed | 10 / 74 (13.51%) | 6 / 73 (8.22%)   |
| occurrences (all)           | 10               | 6                |
| Dysphagia                   |                  |                  |

|                                  |                |                  |
|----------------------------------|----------------|------------------|
| subjects affected / exposed      | 2 / 74 (2.70%) | 2 / 73 (2.74%)   |
| occurrences (all)                | 4              | 3                |
| Enteritis                        |                |                  |
| subjects affected / exposed      | 0 / 74 (0.00%) | 1 / 73 (1.37%)   |
| occurrences (all)                | 0              | 1                |
| Faecal Incontinence              |                |                  |
| subjects affected / exposed      | 1 / 74 (1.35%) | 2 / 73 (2.74%)   |
| occurrences (all)                | 1              | 2                |
| Faeces Discoloured               |                |                  |
| subjects affected / exposed      | 0 / 74 (0.00%) | 1 / 73 (1.37%)   |
| occurrences (all)                | 0              | 1                |
| Faeces Pale                      |                |                  |
| subjects affected / exposed      | 0 / 74 (0.00%) | 1 / 73 (1.37%)   |
| occurrences (all)                | 0              | 1                |
| Flatulence                       |                |                  |
| subjects affected / exposed      | 4 / 74 (5.41%) | 7 / 73 (9.59%)   |
| occurrences (all)                | 4              | 8                |
| Gastritis                        |                |                  |
| subjects affected / exposed      | 2 / 74 (2.70%) | 1 / 73 (1.37%)   |
| occurrences (all)                | 2              | 1                |
| Gastrointestinal Pain            |                |                  |
| subjects affected / exposed      | 0 / 74 (0.00%) | 1 / 73 (1.37%)   |
| occurrences (all)                | 0              | 1                |
| Gastrooesophageal Reflux Disease |                |                  |
| subjects affected / exposed      | 1 / 74 (1.35%) | 3 / 73 (4.11%)   |
| occurrences (all)                | 2              | 3                |
| Gingival Bleeding                |                |                  |
| subjects affected / exposed      | 3 / 74 (4.05%) | 25 / 73 (34.25%) |
| occurrences (all)                | 3              | 30               |
| Gingival Pain                    |                |                  |
| subjects affected / exposed      | 1 / 74 (1.35%) | 4 / 73 (5.48%)   |
| occurrences (all)                | 1              | 5                |
| Glossitis                        |                |                  |
| subjects affected / exposed      | 0 / 74 (0.00%) | 1 / 73 (1.37%)   |
| occurrences (all)                | 0              | 1                |
| Glossodynia                      |                |                  |

|                             |                  |                  |
|-----------------------------|------------------|------------------|
| subjects affected / exposed | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |
| occurrences (all)           | 1                | 0                |
| Haematemesis                |                  |                  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 2 / 73 (2.74%)   |
| occurrences (all)           | 0                | 2                |
| Haematochezia               |                  |                  |
| subjects affected / exposed | 2 / 74 (2.70%)   | 2 / 73 (2.74%)   |
| occurrences (all)           | 2                | 2                |
| Haemorrhoidal Haemorrhage   |                  |                  |
| subjects affected / exposed | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |
| occurrences (all)           | 1                | 0                |
| Haemorrhoids                |                  |                  |
| subjects affected / exposed | 2 / 74 (2.70%)   | 4 / 73 (5.48%)   |
| occurrences (all)           | 3                | 4                |
| Hiatus Hernia               |                  |                  |
| subjects affected / exposed | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |
| occurrences (all)           | 1                | 0                |
| Large Intestine Perforation |                  |                  |
| subjects affected / exposed | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |
| occurrences (all)           | 1                | 0                |
| Melaena                     |                  |                  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)           | 0                | 1                |
| Mesenteric Vein Thrombosis  |                  |                  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)           | 0                | 1                |
| Mouth Haemorrhage           |                  |                  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)           | 0                | 1                |
| Mouth Ulceration            |                  |                  |
| subjects affected / exposed | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |
| occurrences (all)           | 1                | 0                |
| Nausea                      |                  |                  |
| subjects affected / exposed | 27 / 74 (36.49%) | 38 / 73 (52.05%) |
| occurrences (all)           | 43               | 66               |
| Oesophageal Ulcer           |                  |                  |

|                             |                |                 |
|-----------------------------|----------------|-----------------|
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%)  |
| occurrences (all)           | 0              | 1               |
| Oesophagitis                |                |                 |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%)  |
| occurrences (all)           | 1              | 0               |
| Oral Discomfort             |                |                 |
| subjects affected / exposed | 1 / 74 (1.35%) | 1 / 73 (1.37%)  |
| occurrences (all)           | 1              | 1               |
| Oral Disorder               |                |                 |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%)  |
| occurrences (all)           | 0              | 1               |
| Oral Dysaesthesia           |                |                 |
| subjects affected / exposed | 1 / 74 (1.35%) | 2 / 73 (2.74%)  |
| occurrences (all)           | 1              | 3               |
| Oral Mucosal Erythema       |                |                 |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%)  |
| occurrences (all)           | 0              | 1               |
| Oral Pain                   |                |                 |
| subjects affected / exposed | 2 / 74 (2.70%) | 8 / 73 (10.96%) |
| occurrences (all)           | 3              | 9               |
| Paraesthesia Oral           |                |                 |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%)  |
| occurrences (all)           | 0              | 1               |
| Peptic Ulcer                |                |                 |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%)  |
| occurrences (all)           | 1              | 0               |
| Periodontal Disease         |                |                 |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%)  |
| occurrences (all)           | 0              | 1               |
| Proctalgia                  |                |                 |
| subjects affected / exposed | 1 / 74 (1.35%) | 1 / 73 (1.37%)  |
| occurrences (all)           | 1              | 1               |
| Rectal Haemorrhage          |                |                 |
| subjects affected / exposed | 1 / 74 (1.35%) | 3 / 73 (4.11%)  |
| occurrences (all)           | 1              | 3               |
| Retching                    |                |                 |

|                             |                  |                  |  |
|-----------------------------|------------------|------------------|--|
| subjects affected / exposed | 1 / 74 (1.35%)   | 1 / 73 (1.37%)   |  |
| occurrences (all)           | 1                | 1                |  |
| Salivary Hypersecretion     |                  |                  |  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |  |
| occurrences (all)           | 0                | 1                |  |
| Stomatitis                  |                  |                  |  |
| subjects affected / exposed | 8 / 74 (10.81%)  | 18 / 73 (24.66%) |  |
| occurrences (all)           | 11               | 34               |  |
| Swollen Tongue              |                  |                  |  |
| subjects affected / exposed | 1 / 74 (1.35%)   | 1 / 73 (1.37%)   |  |
| occurrences (all)           | 1                | 1                |  |
| Toothache                   |                  |                  |  |
| subjects affected / exposed | 3 / 74 (4.05%)   | 0 / 73 (0.00%)   |  |
| occurrences (all)           | 3                | 0                |  |
| Vomiting                    |                  |                  |  |
| subjects affected / exposed | 14 / 74 (18.92%) | 30 / 73 (41.10%) |  |
| occurrences (all)           | 23               | 57               |  |
| Duodenitis                  |                  |                  |  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 0 / 73 (0.00%)   |  |
| occurrences (all)           | 0                | 0                |  |
| Impaired Gastric Emptying   |                  |                  |  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 0 / 73 (0.00%)   |  |
| occurrences (all)           | 0                | 0                |  |
| Periodontitis               |                  |                  |  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 0 / 73 (0.00%)   |  |
| occurrences (all)           | 0                | 0                |  |
| Hepatobiliary disorders     |                  |                  |  |
| Bile Duct Stenosis          |                  |                  |  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |  |
| occurrences (all)           | 0                | 1                |  |
| Cholelithiasis              |                  |                  |  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |  |
| occurrences (all)           | 0                | 1                |  |
| Gallbladder Pain            |                  |                  |  |
| subjects affected / exposed | 1 / 74 (1.35%)   | 1 / 73 (1.37%)   |  |
| occurrences (all)           | 1                | 1                |  |

|                                        |                |                |  |
|----------------------------------------|----------------|----------------|--|
| Hepatitis                              |                |                |  |
| subjects affected / exposed            | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Liver Disorder                         |                |                |  |
| subjects affected / exposed            | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences (all)                      | 1              | 0              |  |
| Skin and subcutaneous tissue disorders |                |                |  |
| Acne                                   |                |                |  |
| subjects affected / exposed            | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences (all)                      | 1              | 0              |  |
| Actinic Keratosis                      |                |                |  |
| subjects affected / exposed            | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Alopecia                               |                |                |  |
| subjects affected / exposed            | 2 / 74 (2.70%) | 1 / 73 (1.37%) |  |
| occurrences (all)                      | 2              | 1              |  |
| Blister                                |                |                |  |
| subjects affected / exposed            | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences (all)                      | 1              | 0              |  |
| Decubitus Ulcer                        |                |                |  |
| subjects affected / exposed            | 0 / 74 (0.00%) | 2 / 73 (2.74%) |  |
| occurrences (all)                      | 0              | 2              |  |
| Dermatitis                             |                |                |  |
| subjects affected / exposed            | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Dermatitis Acneiform                   |                |                |  |
| subjects affected / exposed            | 2 / 74 (2.70%) | 4 / 73 (5.48%) |  |
| occurrences (all)                      | 2              | 5              |  |
| Dermatitis Bullous                     |                |                |  |
| subjects affected / exposed            | 0 / 74 (0.00%) | 3 / 73 (4.11%) |  |
| occurrences (all)                      | 0              | 6              |  |
| Dry Skin                               |                |                |  |
| subjects affected / exposed            | 3 / 74 (4.05%) | 4 / 73 (5.48%) |  |
| occurrences (all)                      | 3              | 4              |  |
| Erythema                               |                |                |  |

|                                             |                  |                  |
|---------------------------------------------|------------------|------------------|
| subjects affected / exposed                 | 0 / 74 (0.00%)   | 6 / 73 (8.22%)   |
| occurrences (all)                           | 0                | 6                |
| Hyperhidrosis                               |                  |                  |
| subjects affected / exposed                 | 2 / 74 (2.70%)   | 1 / 73 (1.37%)   |
| occurrences (all)                           | 2                | 1                |
| Hyperkeratosis                              |                  |                  |
| subjects affected / exposed                 | 3 / 74 (4.05%)   | 1 / 73 (1.37%)   |
| occurrences (all)                           | 3                | 1                |
| Ingrowing Nail                              |                  |                  |
| subjects affected / exposed                 | 2 / 74 (2.70%)   | 0 / 73 (0.00%)   |
| occurrences (all)                           | 3                | 0                |
| Livedo Reticularis                          |                  |                  |
| subjects affected / exposed                 | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)                           | 0                | 1                |
| Nail Discolouration                         |                  |                  |
| subjects affected / exposed                 | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)                           | 0                | 1                |
| Night Sweats                                |                  |                  |
| subjects affected / exposed                 | 0 / 74 (0.00%)   | 2 / 73 (2.74%)   |
| occurrences (all)                           | 0                | 2                |
| Palmar-plantar Erythrodysaesthesia Syndrome |                  |                  |
| subjects affected / exposed                 | 15 / 74 (20.27%) | 18 / 73 (24.66%) |
| occurrences (all)                           | 61               | 46               |
| Palmoplantar Keratoderma                    |                  |                  |
| subjects affected / exposed                 | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |
| occurrences (all)                           | 1                | 0                |
| Photosensitivity Reaction                   |                  |                  |
| subjects affected / exposed                 | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |
| occurrences (all)                           | 1                | 0                |
| Pruritus                                    |                  |                  |
| subjects affected / exposed                 | 2 / 74 (2.70%)   | 3 / 73 (4.11%)   |
| occurrences (all)                           | 2                | 6                |
| Purpura                                     |                  |                  |
| subjects affected / exposed                 | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)                           | 0                | 1                |

|                             |                |                  |
|-----------------------------|----------------|------------------|
| Rash                        |                |                  |
| subjects affected / exposed | 6 / 74 (8.11%) | 12 / 73 (16.44%) |
| occurrences (all)           | 14             | 15               |
| Rash Erythematous           |                |                  |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%)   |
| occurrences (all)           | 0              | 1                |
| Rash Macular                |                |                  |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%)   |
| occurrences (all)           | 0              | 1                |
| Rash Maculo-papular         |                |                  |
| subjects affected / exposed | 1 / 74 (1.35%) | 6 / 73 (8.22%)   |
| occurrences (all)           | 1              | 5                |
| Rash Pruritic               |                |                  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%)   |
| occurrences (all)           | 1              | 0                |
| Rosacea                     |                |                  |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%)   |
| occurrences (all)           | 0              | 1                |
| Scab                        |                |                  |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%)   |
| occurrences (all)           | 0              | 1                |
| Skin Discolouration         |                |                  |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%)   |
| occurrences (all)           | 0              | 1                |
| Skin Erosion                |                |                  |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%)   |
| occurrences (all)           | 0              | 1                |
| Skin Exfoliation            |                |                  |
| subjects affected / exposed | 3 / 74 (4.05%) | 0 / 73 (0.00%)   |
| occurrences (all)           | 4              | 0                |
| Skin Hyperpigmentation      |                |                  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%)   |
| occurrences (all)           | 1              | 0                |
| Skin Lesion                 |                |                  |
| subjects affected / exposed | 1 / 74 (1.35%) | 1 / 73 (1.37%)   |
| occurrences (all)           | 1              | 1                |

|                             |                |                 |  |
|-----------------------------|----------------|-----------------|--|
| Skin Ulcer                  |                |                 |  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%)  |  |
| occurrences (all)           | 1              | 0               |  |
| Subcutaneous Nodule         |                |                 |  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%)  |  |
| occurrences (all)           | 1              | 0               |  |
| Swelling Face               |                |                 |  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%)  |  |
| occurrences (all)           | 1              | 0               |  |
| Telangiectasia              |                |                 |  |
| subjects affected / exposed | 0 / 74 (0.00%) | 5 / 73 (6.85%)  |  |
| occurrences (all)           | 0              | 5               |  |
| Petechiae                   |                |                 |  |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 73 (0.00%)  |  |
| occurrences (all)           | 0              | 0               |  |
| Renal and urinary disorders |                |                 |  |
| Acute Kidney Injury         |                |                 |  |
| subjects affected / exposed | 2 / 74 (2.70%) | 1 / 73 (1.37%)  |  |
| occurrences (all)           | 2              | 2               |  |
| Bladder Spasm               |                |                 |  |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%)  |  |
| occurrences (all)           | 0              | 1               |  |
| Dysuria                     |                |                 |  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%)  |  |
| occurrences (all)           | 1              | 0               |  |
| Glycosuria                  |                |                 |  |
| subjects affected / exposed | 2 / 74 (2.70%) | 0 / 73 (0.00%)  |  |
| occurrences (all)           | 3              | 0               |  |
| Haematuria                  |                |                 |  |
| subjects affected / exposed | 2 / 74 (2.70%) | 8 / 73 (10.96%) |  |
| occurrences (all)           | 2              | 8               |  |
| Hydronephrosis              |                |                 |  |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%)  |  |
| occurrences (all)           | 0              | 1               |  |
| Micturition Urgency         |                |                 |  |

|                              |                  |                |  |
|------------------------------|------------------|----------------|--|
| subjects affected / exposed  | 0 / 74 (0.00%)   | 2 / 73 (2.74%) |  |
| occurrences (all)            | 0                | 2              |  |
| Nephrolithiasis              |                  |                |  |
| subjects affected / exposed  | 0 / 74 (0.00%)   | 1 / 73 (1.37%) |  |
| occurrences (all)            | 0                | 1              |  |
| Pollakiuria                  |                  |                |  |
| subjects affected / exposed  | 2 / 74 (2.70%)   | 1 / 73 (1.37%) |  |
| occurrences (all)            | 2                | 1              |  |
| Proteinuria                  |                  |                |  |
| subjects affected / exposed  | 15 / 74 (20.27%) | 3 / 73 (4.11%) |  |
| occurrences (all)            | 29               | 4              |  |
| Renal Failure                |                  |                |  |
| subjects affected / exposed  | 0 / 74 (0.00%)   | 2 / 73 (2.74%) |  |
| occurrences (all)            | 0                | 3              |  |
| Urethral Meatus Stenosis     |                  |                |  |
| subjects affected / exposed  | 0 / 74 (0.00%)   | 1 / 73 (1.37%) |  |
| occurrences (all)            | 0                | 1              |  |
| Urinary Incontinence         |                  |                |  |
| subjects affected / exposed  | 2 / 74 (2.70%)   | 2 / 73 (2.74%) |  |
| occurrences (all)            | 2                | 2              |  |
| Urinary Retention            |                  |                |  |
| subjects affected / exposed  | 1 / 74 (1.35%)   | 2 / 73 (2.74%) |  |
| occurrences (all)            | 1                | 2              |  |
| Urinary Tract Pain           |                  |                |  |
| subjects affected / exposed  | 1 / 74 (1.35%)   | 0 / 73 (0.00%) |  |
| occurrences (all)            | 1                | 0              |  |
| Incontinence                 |                  |                |  |
| subjects affected / exposed  | 0 / 74 (0.00%)   | 0 / 73 (0.00%) |  |
| occurrences (all)            | 0                | 0              |  |
| Endocrine disorders          |                  |                |  |
| Adrenal Insufficiency        |                  |                |  |
| subjects affected / exposed  | 0 / 74 (0.00%)   | 1 / 73 (1.37%) |  |
| occurrences (all)            | 0                | 1              |  |
| Hypercalcaemia of malignancy |                  |                |  |
| subjects affected / exposed  | 1 / 74 (1.35%)   | 0 / 73 (0.00%) |  |
| occurrences (all)            | 1                | 0              |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| Hyperthyroidism                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |  |
| occurrences (all)                               | 1                | 0                |  |
| Hypothyroidism                                  |                  |                  |  |
| subjects affected / exposed                     | 20 / 74 (27.03%) | 17 / 73 (23.29%) |  |
| occurrences (all)                               | 25               | 18               |  |
| Thyroid Disorder                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |  |
| occurrences (all)                               | 0                | 1                |  |
| Musculoskeletal and connective tissue disorders |                  |                  |  |
| Arthralgia                                      |                  |                  |  |
| subjects affected / exposed                     | 10 / 74 (13.51%) | 8 / 73 (10.96%)  |  |
| occurrences (all)                               | 18               | 15               |  |
| Back Pain                                       |                  |                  |  |
| subjects affected / exposed                     | 17 / 74 (22.97%) | 7 / 73 (9.59%)   |  |
| occurrences (all)                               | 19               | 10               |  |
| Bone Pain                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 74 (0.00%)   | 3 / 73 (4.11%)   |  |
| occurrences (all)                               | 0                | 3                |  |
| Flank Pain                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 74 (2.70%)   | 5 / 73 (6.85%)   |  |
| occurrences (all)                               | 3                | 6                |  |
| Groin Pain                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 74 (2.70%)   | 1 / 73 (1.37%)   |  |
| occurrences (all)                               | 2                | 1                |  |
| Inguinal Mass                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |  |
| occurrences (all)                               | 0                | 1                |  |
| Joint Swelling                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |  |
| occurrences (all)                               | 1                | 0                |  |
| Muscle Spasms                                   |                  |                  |  |
| subjects affected / exposed                     | 3 / 74 (4.05%)   | 2 / 73 (2.74%)   |  |
| occurrences (all)                               | 3                | 2                |  |
| Muscular Weakness                               |                  |                  |  |

|                             |                |                  |
|-----------------------------|----------------|------------------|
| subjects affected / exposed | 4 / 74 (5.41%) | 4 / 73 (5.48%)   |
| occurrences (all)           | 6              | 6                |
| Musculoskeletal Chest Pain  |                |                  |
| subjects affected / exposed | 5 / 74 (6.76%) | 3 / 73 (4.11%)   |
| occurrences (all)           | 6              | 4                |
| Musculoskeletal Pain        |                |                  |
| subjects affected / exposed | 6 / 74 (8.11%) | 5 / 73 (6.85%)   |
| occurrences (all)           | 6              | 6                |
| Myalgia                     |                |                  |
| subjects affected / exposed | 5 / 74 (6.76%) | 7 / 73 (9.59%)   |
| occurrences (all)           | 5              | 9                |
| Neck Pain                   |                |                  |
| subjects affected / exposed | 4 / 74 (5.41%) | 2 / 73 (2.74%)   |
| occurrences (all)           | 4              | 5                |
| Osteoarthritis              |                |                  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%)   |
| occurrences (all)           | 5              | 0                |
| Osteoporosis                |                |                  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%)   |
| occurrences (all)           | 1              | 0                |
| Pain In Extremity           |                |                  |
| subjects affected / exposed | 6 / 74 (8.11%) | 14 / 73 (19.18%) |
| occurrences (all)           | 10             | 18               |
| Pain In Jaw                 |                |                  |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%)   |
| occurrences (all)           | 0              | 2                |
| Pathological Fracture       |                |                  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%)   |
| occurrences (all)           | 1              | 0                |
| Plantar Fasciitis           |                |                  |
| subjects affected / exposed | 1 / 74 (1.35%) | 1 / 73 (1.37%)   |
| occurrences (all)           | 1              | 1                |
| Spondylolisthesis           |                |                  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%)   |
| occurrences (all)           | 1              | 0                |
| Tendonitis                  |                |                  |

|                             |                |                |  |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |
| Musculoskeletal Stiffness   |                |                |  |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 73 (0.00%) |  |
| occurrences (all)           | 0              | 0              |  |
| Infections and infestations |                |                |  |
| Anal Abscess                |                |                |  |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences (all)           | 0              | 1              |  |
| Bronchitis                  |                |                |  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |
| Candidiasis                 |                |                |  |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences (all)           | 0              | 1              |  |
| Cellulitis                  |                |                |  |
| subjects affected / exposed | 1 / 74 (1.35%) | 1 / 73 (1.37%) |  |
| occurrences (all)           | 1              | 1              |  |
| Cystitis                    |                |                |  |
| subjects affected / exposed | 1 / 74 (1.35%) | 3 / 73 (4.11%) |  |
| occurrences (all)           | 1              | 3              |  |
| Dacryocanaliculitis         |                |                |  |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences (all)           | 0              | 1              |  |
| Diarrhoea Infectious        |                |                |  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |
| Folliculitis                |                |                |  |
| subjects affected / exposed | 0 / 74 (0.00%) | 2 / 73 (2.74%) |  |
| occurrences (all)           | 0              | 2              |  |
| Fungal Infection            |                |                |  |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%) |  |
| occurrences (all)           | 0              | 1              |  |
| Fungal Skin Infection       |                |                |  |
| subjects affected / exposed | 1 / 74 (1.35%) | 2 / 73 (2.74%) |  |
| occurrences (all)           | 2              | 2              |  |

|                             |                |                |
|-----------------------------|----------------|----------------|
| Furuncle                    |                |                |
| subjects affected / exposed | 0 / 74 (0.00%) | 2 / 73 (2.74%) |
| occurrences (all)           | 0              | 2              |
| Gingival Infection          |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Incision Site Infection     |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Influenza                   |                |                |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%) |
| occurrences (all)           | 0              | 1              |
| Kidney Infection            |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Lung Infection              |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Lymph Gland Infection       |                |                |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%) |
| occurrences (all)           | 0              | 1              |
| Nail Infection              |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Nasopharyngitis             |                |                |
| subjects affected / exposed | 4 / 74 (5.41%) | 3 / 73 (4.11%) |
| occurrences (all)           | 4              | 3              |
| Oral Candidiasis            |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Oral Herpes                 |                |                |
| subjects affected / exposed | 0 / 74 (0.00%) | 4 / 73 (5.48%) |
| occurrences (all)           | 0              | 6              |
| Otitis Externa              |                |                |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%) |
| occurrences (all)           | 0              | 1              |

|                             |                |                |
|-----------------------------|----------------|----------------|
| Otitis Media                |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Paronychia                  |                |                |
| subjects affected / exposed | 2 / 74 (2.70%) | 0 / 73 (0.00%) |
| occurrences (all)           | 2              | 0              |
| Pharyngitis                 |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 1 / 73 (1.37%) |
| occurrences (all)           | 1              | 1              |
| Platelet Count Decreased    |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Pneumonia                   |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 3 / 73 (4.11%) |
| occurrences (all)           | 1              | 3              |
| Sepsis                      |                |                |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%) |
| occurrences (all)           | 0              | 1              |
| Sinusitis                   |                |                |
| subjects affected / exposed | 6 / 74 (8.11%) | 3 / 73 (4.11%) |
| occurrences (all)           | 7              | 5              |
| Skin Infection              |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 1 / 73 (1.37%) |
| occurrences (all)           | 1              | 1              |
| Staphylococcal Infection    |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Tinea Cruris                |                |                |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%) |
| occurrences (all)           | 2              | 0              |
| Tinea Pedis                 |                |                |
| subjects affected / exposed | 2 / 74 (2.70%) | 0 / 73 (0.00%) |
| occurrences (all)           | 3              | 0              |
| Tinea Versicolour           |                |                |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%) |
| occurrences (all)           | 0              | 1              |

|                                                                                       |                      |                     |  |
|---------------------------------------------------------------------------------------|----------------------|---------------------|--|
| Tooth Abscess<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 74 (0.00%)<br>0  | 3 / 73 (4.11%)<br>4 |  |
| Tooth Infection<br>subjects affected / exposed<br>occurrences (all)                   | 4 / 74 (5.41%)<br>4  | 1 / 73 (1.37%)<br>1 |  |
| Upper Respiratory Infection<br>subjects affected / exposed<br>occurrences (all)       | 8 / 74 (10.81%)<br>9 | 6 / 73 (8.22%)<br>9 |  |
| Upper Respiratory Tract Infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 74 (1.35%)<br>1  | 1 / 73 (1.37%)<br>1 |  |
| Urinary Tract Infection<br>subjects affected / exposed<br>occurrences (all)           | 4 / 74 (5.41%)<br>5  | 5 / 73 (6.85%)<br>5 |  |
| Vaginal Infection<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 74 (1.35%)<br>1  | 1 / 73 (1.37%)<br>1 |  |
| Viral Infection<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 74 (0.00%)<br>0  | 1 / 73 (1.37%)<br>1 |  |
| Vulvovaginal Mycotic Infection<br>subjects affected / exposed<br>occurrences (all)    | 0 / 74 (0.00%)<br>0  | 1 / 73 (1.37%)<br>1 |  |
| Wound Infection<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 74 (1.35%)<br>1  | 0 / 73 (0.00%)<br>0 |  |
| Nasal Vestibulitis<br>subjects affected / exposed<br>occurrences (all)                | 0 / 74 (0.00%)<br>0  | 0 / 73 (0.00%)<br>0 |  |
| Pneumonial Staphylococcal<br>subjects affected / exposed<br>occurrences (all)         | 0 / 74 (0.00%)<br>0  | 0 / 73 (0.00%)<br>0 |  |
| Metabolism and nutrition disorders<br>Cachexia                                        |                      |                     |  |

|                             |                  |                  |
|-----------------------------|------------------|------------------|
| subjects affected / exposed | 1 / 74 (1.35%)   | 2 / 73 (2.74%)   |
| occurrences (all)           | 1                | 2                |
| Decreased Appetite          |                  |                  |
| subjects affected / exposed | 26 / 74 (35.14%) | 21 / 73 (28.77%) |
| occurrences (all)           | 34               | 40               |
| Dehydration                 |                  |                  |
| subjects affected / exposed | 7 / 74 (9.46%)   | 11 / 73 (15.07%) |
| occurrences (all)           | 15               | 19               |
| Glucose Tolerance Impaired  |                  |                  |
| subjects affected / exposed | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |
| occurrences (all)           | 1                | 0                |
| Hypercalcaemia              |                  |                  |
| subjects affected / exposed | 5 / 74 (6.76%)   | 2 / 73 (2.74%)   |
| occurrences (all)           | 13               | 2                |
| Hypercholesterolaemia       |                  |                  |
| subjects affected / exposed | 1 / 74 (1.35%)   | 0 / 73 (0.00%)   |
| occurrences (all)           | 1                | 0                |
| Hyperglycaemia              |                  |                  |
| subjects affected / exposed | 6 / 74 (8.11%)   | 5 / 73 (6.85%)   |
| occurrences (all)           | 14               | 14               |
| Hyperkalaemia               |                  |                  |
| subjects affected / exposed | 1 / 74 (1.35%)   | 2 / 73 (2.74%)   |
| occurrences (all)           | 2                | 1                |
| Hypernatraemia              |                  |                  |
| subjects affected / exposed | 0 / 74 (0.00%)   | 1 / 73 (1.37%)   |
| occurrences (all)           | 0                | 1                |
| Hyperuricaemia              |                  |                  |
| subjects affected / exposed | 2 / 74 (2.70%)   | 0 / 73 (0.00%)   |
| occurrences (all)           | 2                | 0                |
| Hypoalbuminaemia            |                  |                  |
| subjects affected / exposed | 3 / 74 (4.05%)   | 5 / 73 (6.85%)   |
| occurrences (all)           | 5                | 7                |
| Hypocalcaemia               |                  |                  |
| subjects affected / exposed | 2 / 74 (2.70%)   | 2 / 73 (2.74%)   |
| occurrences (all)           | 2                | 2                |
| Hypoglycaemia               |                  |                  |

|                             |                |                  |
|-----------------------------|----------------|------------------|
| subjects affected / exposed | 1 / 74 (1.35%) | 1 / 73 (1.37%)   |
| occurrences (all)           | 1              | 2                |
| Hypokalaemia                |                |                  |
| subjects affected / exposed | 4 / 74 (5.41%) | 3 / 73 (4.11%)   |
| occurrences (all)           | 8              | 4                |
| Hypomagnesaemia             |                |                  |
| subjects affected / exposed | 2 / 74 (2.70%) | 2 / 73 (2.74%)   |
| occurrences (all)           | 2              | 2                |
| Hyponatraemia               |                |                  |
| subjects affected / exposed | 5 / 74 (6.76%) | 12 / 73 (16.44%) |
| occurrences (all)           | 5              | 17               |
| Hypophosphataemia           |                |                  |
| subjects affected / exposed | 6 / 74 (8.11%) | 3 / 73 (4.11%)   |
| occurrences (all)           | 7              | 3                |
| Hypoproteinaemia            |                |                  |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 73 (1.37%)   |
| occurrences (all)           | 0              | 1                |
| Hypovolaemia                |                |                  |
| subjects affected / exposed | 2 / 74 (2.70%) | 0 / 73 (0.00%)   |
| occurrences (all)           | 3              | 0                |
| Type 2 Diabetes Mellitus    |                |                  |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 73 (0.00%)   |
| occurrences (all)           | 1              | 0                |
| Hyperphosphataemia          |                |                  |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 73 (0.00%)   |
| occurrences (all)           | 0              | 0                |
| Hypertriglyceridaemia       |                |                  |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 73 (0.00%)   |
| occurrences (all)           | 0              | 0                |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

|                                                                                                                                                                                                   |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| The study was terminated early due to lack of efficacy therefore protein biomarkers (P1b and P2), PK (P2) and disease control rate at 16 weeks by RECIST 1.1 and Choi criteria were not analyzed. |
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Notes: