



## Clinical trial results:

**An open-label early access phase IIIb study of trifluridine / tipiracil (S 95005/TAS-102) in patients with a pretreated metastatic colorectal cancer (PRECONNECT study).**

### Summary

|                          |                                  |
|--------------------------|----------------------------------|
| EudraCT number           | 2016-002311-18                   |
| Trial protocol           | ES BE PT PL SI FR SK BG HR IT RO |
| Global end of trial date | 30 November 2020                 |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 06 November 2021 |
| First version publication date | 06 November 2021 |

### Trial information

#### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | CL3-95005-004 |
|-----------------------|---------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03306394 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Institut de Recherches Internationales Servier   |
| Sponsor organisation address | 50 rue Carnot, Suresnes, France, 92284   |
| Public contact               | Clinical Studies Department, Institut de Recherches Internationales Servier, +33 1.55.72.43.66, clinicaltrials@servier.com |
| Scientific contact           | Clinical Studies Department, Institut de Recherches Internationales Servier, +33 1.55.72.43.66, clinicaltrials@servier.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 30 November 2020 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 30 November 2020 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 30 November 2020 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to collect additional safety data during treatment with trifluridine / tipiracil in patients with a pretreated metastatic colorectal cancer (mCRC).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 03 November 2016 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |               |
|--------------------------------------|---------------|
| Country: Number of subjects enrolled | Australia: 70 |
| Country: Number of subjects enrolled | Brazil: 55    |
| Country: Number of subjects enrolled | Panama: 17    |
| Country: Number of subjects enrolled | Turkey: 100   |
| Country: Number of subjects enrolled | Ukraine: 12   |
| Country: Number of subjects enrolled | Belgium: 45   |
| Country: Number of subjects enrolled | Bulgaria: 12  |
| Country: Number of subjects enrolled | Croatia: 16   |
| Country: Number of subjects enrolled | France: 292   |
| Country: Number of subjects enrolled | Ireland: 7    |
| Country: Number of subjects enrolled | Italy: 161    |
| Country: Number of subjects enrolled | Poland: 54    |
| Country: Number of subjects enrolled | Portugal: 24  |
| Country: Number of subjects enrolled | Romania: 30   |
| Country: Number of subjects enrolled | Slovakia: 15  |
| Country: Number of subjects enrolled | Slovenia: 4   |
| Worldwide total number of subjects   | 914           |
| EEA total number of subjects         | 660           |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 525 |
| From 65 to 84 years                       | 387 |
| 85 years and over                         | 2   |

## Subject disposition

### Recruitment

Recruitment details:

Investigators were oncologists.

### Pre-assignment

Screening details:

Male or female patients aged  $\geq 18$  years old with metastatic colorectal cancer (mCRC) previously treated by at least 2 prior regimens of standard chemotherapies for mCRC and was refractory or intolerant to those chemotherapies.

Of note, 916 patients were enrolled in the study: 914 were treated and 2 not treated.

### Period 1

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

### Arms

|  |                        |
|--|------------------------|
| Arm title                              | S95005                 |
| Arm description: -                     |                        |
| Arm type                               | Experimental           |
| Investigational medicinal product name | S95005                 |
| Investigational medicinal product code |                        |
| Other name                             | Trifluridine-tipiracil |
| Pharmaceutical forms                   | Film-coated tablet     |
| Routes of administration               | Oral use               |

Dosage and administration details:

S95005 was administered orally twice a day (35 mg/m<sup>2</sup>/dose) within 1 hour after completion of morning and evening meals, 5 days on/2 days off, over 2 weeks, followed by a 14-day rest.

| Number of subjects in period 1         | S95005 |
|--|--------|
| Started                                | 914    |
| Completed                              | 0      |
| Not completed                          | 914    |
| Physician decision                     | 14     |
| Adverse event, non-fatal               | 55     |
| Study termination by sponsor           | 20     |
| Progressive disease                    | 736    |
| Commercial availability of the product | 68     |
| Lost to follow-up                      | 3      |
| Non-medical reason                     | 18     |



## Baseline characteristics

### Reporting groups

|                       |        |
|-----------------------|--------|
| Reporting group title | S95005 |
|-----------------------|--------|

Reporting group description: -

| Reporting group values | S95005 | Total |  |
|------------------------|--------|-------|--|
| Number of subjects     | 914    | 914   |  |
| Age categorical        |        |       |  |
| Units: Subjects        |        |       |  |
| Adults (18-64 years)   | 525    | 525   |  |
| From 65-84 years       | 387    | 387   |  |
| 85 years and over      | 2      | 2     |  |
| Age continuous         |        |       |  |
| Units: years           |        |       |  |
| arithmetic mean        | 61.5   |       |  |
| standard deviation     | ± 10.6 | -     |  |
| Gender categorical     |        |       |  |
| Units: Subjects        |        |       |  |
| Female                 | 373    | 373   |  |
| Male                   | 541    | 541   |  |

## End points

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### End points reporting groups

|                       |        |
|-----------------------|--------|
| Reporting group title | S95005 |
|-----------------------|--------|

Reporting group description: -

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### Primary: Adverse events

|                 |                               |
|-----------------|-------------------------------|
| End point title | Adverse events <sup>[1]</sup> |
|-----------------|-------------------------------|

End point description:

The primary objective of this study was to collect additional safety data during treatment with trifluridine/tipiracil in patients with a pretreated mCRC.

The number of subjects affected by adverse events is given in the present endpoints section. Description of serious and non-serious adverse events is provided in the adverse events section.

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

End point timeframe:

See the section adverse events.

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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: No statistical analyses for this end point

| End point values                   | S95005          |  |  |  |
|------------------------------------|-----------------|--|--|--|
| Subject group type                 | Reporting group |  |  |  |
| Number of subjects analysed        | 914             |  |  |  |
| Units: Number of patients affected |                 |  |  |  |
| number (not applicable)            | 884             |  |  |  |

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### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All adverse events that occurred or worsened or became serious between the first and the last IMP intake + 35 days (both included).

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 23.0   |

### Reporting groups

|                       |        |
|-----------------------|--------|
| Reporting group title | S95005 |
|-----------------------|--------|

Reporting group description: -

| Serious adverse events  | S95005             |  |  |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events                   |                    |  |  |
| subjects affected / exposed   | 335 / 914 (36.65%) |  |  |
| number of deaths (all causes)                                       | 87                 |  |  |
| number of deaths resulting from adverse events                      | 3                  |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |  |  |
| Cancer pain   |                    |  |  |
| subjects affected / exposed   | 9 / 914 (0.98%)    |  |  |
| occurrences causally related to treatment / all                     | 0 / 10             |  |  |
| deaths causally related to treatment / all                          | 0 / 0              |  |  |
| Intracranial tumour haemorrhage                                     |                    |  |  |
| subjects affected / exposed   | 1 / 914 (0.11%)    |  |  |
| occurrences causally related to treatment / all                     | 0 / 1              |  |  |
| deaths causally related to treatment / all                          | 0 / 1              |  |  |
| Malignant ascites   |                    |  |  |
| subjects affected / exposed   | 2 / 914 (0.22%)    |  |  |
| occurrences causally related to treatment / all                     | 0 / 2              |  |  |
| deaths causally related to treatment / all                          | 0 / 0              |  |  |
| Malignant neoplasm progression                                      |                    |  |  |
| subjects affected / exposed   | 124 / 914 (13.57%) |  |  |
| occurrences causally related to treatment / all                     | 3 / 124            |  |  |
| deaths causally related to treatment / all                          | 2 / 54             |  |  |
| Malignant pleural effusion  |                    |  |  |



|   |                  |  |  |  |
|---|------------------|--|--|--|
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Metastases to biliary tract                     |                  |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Metastases to bladder                           |                  |  |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Metastases to bone                              |                  |  |  |  |
| subjects affected / exposed                     | 3 / 914 (0.33%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Metastases to central nervous system            |                  |  |  |  |
| subjects affected / exposed                     | 20 / 914 (2.19%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 20           |  |  |  |
| deaths causally related to treatment / all      | 0 / 3            |  |  |  |
| Metastases to kidney                            |                  |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Metastases to liver                             |                  |  |  |  |
| subjects affected / exposed                     | 3 / 914 (0.33%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Metastases to lung                              |                  |  |  |  |
| subjects affected / exposed                     | 4 / 914 (0.44%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |  |
| deaths causally related to treatment / all      | 0 / 3            |  |  |  |
| Metastases to muscle                            |                  |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metastases to peritoneum                        |                 |  |  |
| subjects affected / exposed                     | 3 / 914 (0.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metastases to pleura                            |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Metastases to retroperitoneum                   |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metastases to spine                             |                 |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tumour associated fever                         |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metastasis                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tumour compression                              |                 |  |  |
| subjects affected / exposed                     | 3 / 914 (0.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vascular disorders                              |                 |  |  |
| Aortic aneurysm                                 |                 |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                          | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 1           |  |  |
| Hypertension   |                 |  |  |
| subjects affected / exposed                          | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Deep vein thrombosis                                 |                 |  |  |
| subjects affected / exposed                          | 6 / 914 (0.66%) |  |  |
| occurrences causally related to treatment / all      | 1 / 6           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Jugular vein thrombosis                              |                 |  |  |
| subjects affected / exposed                          | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Hypotension  |                 |  |  |
| subjects affected / exposed                          | 3 / 914 (0.33%) |  |  |
| occurrences causally related to treatment / all      | 1 / 3           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Thrombosis   |                 |  |  |
| subjects affected / exposed                          | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Asthenia   |                 |  |  |
| subjects affected / exposed                          | 3 / 914 (0.33%) |  |  |
| occurrences causally related to treatment / all      | 2 / 3           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Death  |                 |  |  |
| subjects affected / exposed                          | 5 / 914 (0.55%) |  |  |
| occurrences causally related to treatment / all      | 1 / 5           |  |  |
| deaths causally related to treatment / all           | 1 / 5           |  |  |
| Chest pain   |                 |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Fatigue</b>                                  |                  |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%)  |  |  |
| occurrences causally related to treatment / all | 2 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Generalised oedema</b>                       |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| <b>General physical health deterioration</b>    |                  |  |  |
| subjects affected / exposed                     | 20 / 914 (2.19%) |  |  |
| occurrences causally related to treatment / all | 3 / 20           |  |  |
| deaths causally related to treatment / all      | 0 / 8            |  |  |
| <b>Multiple organ dysfunction syndrome</b>      |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| <b>Oedema peripheral</b>                        |                  |  |  |
| subjects affected / exposed                     | 3 / 914 (0.33%)  |  |  |
| occurrences causally related to treatment / all | 1 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Pyrexia</b>                                  |                  |  |  |
| subjects affected / exposed                     | 8 / 914 (0.88%)  |  |  |
| occurrences causally related to treatment / all | 2 / 8            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Systemic inflammatory response syndrome</b>  |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Reproductive system and breast disorders</b> |                  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Perineal induration                             |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Prostatitis                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Bronchospasm                                    |                 |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Acute respiratory failure                       |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Bronchopleural fistula                          |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dyspnoea  |                 |  |  |
| subjects affected / exposed                     | 4 / 914 (0.44%) |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Epistaxis                                       |                 |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haemoptysis                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| Interstitial lung disease                       |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pleural effusion                                |                  |  |  |
| subjects affected / exposed                     | 8 / 914 (0.88%)  |  |  |
| occurrences causally related to treatment / all | 0 / 8            |  |  |
| deaths causally related to treatment / all      | 0 / 3            |  |  |
| Pulmonary embolism                              |                  |  |  |
| subjects affected / exposed                     | 10 / 914 (1.09%) |  |  |
| occurrences causally related to treatment / all | 2 / 10           |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pulmonary infarction                            |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pulmonary oedema                                |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Respiratory distress                            |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Respiratory failure                             |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Psychiatric disorders                           |                  |  |  |
| Anxiety disorder                                |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Confusional state                               |                  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 2 / 914 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Delirium tremens                                |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Delirium  |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hallucination                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Product issues                                  |                 |  |  |
| Device occlusion                                |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Investigations                                  |                 |  |  |
| Alanine aminotransferase increased              |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Aspartate aminotransferase increased            |                 |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood alkaline phosphatase increased            |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Blood creatinine increased                      |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gamma-glutamyltransferase increased             |                 |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Neutrophil count decreased                      |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Platelet count decreased                        |                 |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%) |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Weight decreased                                |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| Anaemia postoperative                           |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bladder injury                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Facial bones fracture                           |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| Fall  |                 |  |  |
| subjects affected / exposed                     | 5 / 914 (0.55%) |  |  |
| occurrences causally related to treatment / all | 0 / 5           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Femur fracture                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lumbar vertebral fracture                       |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Incision site haematoma                         |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Upper limb fracture                             |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urinary tract stoma complication                |                 |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vascular access malfunction                     |                 |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Acute myocardial infarction                     |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atrial fibrillation                             |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 3 / 914 (0.33%) |  |  |
| occurrences causally related to treatment / all | 1 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pericardial effusion                            |                 |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 2           |  |  |
| Myocardial infarction                           |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tachycardia                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Nervous system disorders                        |                 |  |  |
| Coma hepatic                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Apraxia   |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cauda equina syndrome                           |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dizziness                                       |                 |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Epilepsy  |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Headache  |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haemorrhage intracranial                        |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Febrile convulsion                              |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Neuralgia                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Loss of consciousness                           |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intracranial aneurysm                           |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Status epilepticus                              |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Neuropathy peripheral                           |                 |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Sciatica  |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Syncope   |                  |  |  |
| subjects affected / exposed                     | 3 / 914 (0.33%)  |  |  |
| occurrences causally related to treatment / all | 1 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Transient ischaemic attack                      |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vertigo CNS origin                              |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Blood and lymphatic system disorders            |                  |  |  |
| Anaemia   |                  |  |  |
| subjects affected / exposed                     | 34 / 914 (3.72%) |  |  |
| occurrences causally related to treatment / all | 28 / 37          |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Blood loss anaemia                              |                  |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%)  |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Anaemia of malignant disease                    |                  |  |  |
| subjects affected / exposed                     | 4 / 914 (0.44%)  |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Bone marrow failure                             |                  |  |  |

|   |                  |  |  |  |
|---|------------------|--|--|--|
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Febrile bone marrow aplasia                     |                  |  |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%)  |  |  |  |
| occurrences causally related to treatment / all | 2 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Febrile neutropenia                             |                  |  |  |  |
| subjects affected / exposed                     | 9 / 914 (0.98%)  |  |  |  |
| occurrences causally related to treatment / all | 10 / 10          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Microcytic anaemia                              |                  |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Leukopenia                                      |                  |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Lymphopenia                                     |                  |  |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%)  |  |  |  |
| occurrences causally related to treatment / all | 2 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Pancytopenia                                    |                  |  |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%)  |  |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Neutropenia                                     |                  |  |  |  |
| subjects affected / exposed                     | 20 / 914 (2.19%) |  |  |  |
| occurrences causally related to treatment / all | 25 / 25          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Thrombocytopenia                                |                  |  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 5 / 914 (0.55%)  |  |  |
| occurrences causally related to treatment / all | 4 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Eye disorders                                   |                  |  |  |
| Blindness unilateral                            |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Retinal artery thrombosis                       |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastrointestinal disorders                      |                  |  |  |
| Abdominal hernia                                |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Abdominal incarcerated hernia                   |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Abdominal pain                                  |                  |  |  |
| subjects affected / exposed                     | 12 / 914 (1.31%) |  |  |
| occurrences causally related to treatment / all | 2 / 13           |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Abdominal pain upper                            |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Abdominal pain lower                            |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Abdominal strangulated hernia                   |                  |  |  |

|   |                  |  |  |  |
|---|------------------|--|--|--|
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Ascites   |                  |  |  |  |
| subjects affected / exposed                     | 11 / 914 (1.20%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 11           |  |  |  |
| deaths causally related to treatment / all      | 0 / 2            |  |  |  |
| Anal haemorrhage                                |                  |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Constipation                                    |                  |  |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Colitis   |                  |  |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%)  |  |  |  |
| occurrences causally related to treatment / all | 2 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Diarrhoea                                       |                  |  |  |  |
| subjects affected / exposed                     | 11 / 914 (1.20%) |  |  |  |
| occurrences causally related to treatment / all | 11 / 12          |  |  |  |
| deaths causally related to treatment / all      | 1 / 1            |  |  |  |
| Dysphagia                                       |                  |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Enteritis                                       |                  |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Faecaloma                                       |                  |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 2 / 914 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastric stenosis                                |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal haemorrhage                    |                 |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal obstruction                    |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal toxicity                       |                 |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%) |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haemorrhoidal haemorrhage                       |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ileus paralytic                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ileus   |                 |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Impaired gastric emptying                       |                 |  |  |



|   |                  |  |  |  |
|---|------------------|--|--|--|
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Intestinal obstruction                          |                  |  |  |  |
| subjects affected / exposed                     | 16 / 914 (1.75%) |  |  |  |
| occurrences causally related to treatment / all | 2 / 16           |  |  |  |
| deaths causally related to treatment / all      | 0 / 3            |  |  |  |
| Intestinal perforation                          |                  |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |  |
| Large intestinal stenosis                       |                  |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Malignant gastrointestinal obstruction          |                  |  |  |  |
| subjects affected / exposed                     | 3 / 914 (0.33%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |  |
| Mouth ulceration                                |                  |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Obstruction gastric                             |                  |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Nausea  |                  |  |  |  |
| subjects affected / exposed                     | 3 / 914 (0.33%)  |  |  |  |
| occurrences causally related to treatment / all | 2 / 5            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Oesophageal varices haemorrhage                 |                  |  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pancreatic failure                              |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pancreatitis                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Peritoneocutaneous fistula                      |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Stomatitis                                      |                  |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%)  |  |  |
| occurrences causally related to treatment / all | 2 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Subileus  |                  |  |  |
| subjects affected / exposed                     | 6 / 914 (0.66%)  |  |  |
| occurrences causally related to treatment / all | 2 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Varices oesophageal                             |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vomiting  |                  |  |  |
| subjects affected / exposed                     | 14 / 914 (1.53%) |  |  |
| occurrences causally related to treatment / all | 8 / 16           |  |  |
| deaths causally related to treatment / all      | 1 / 2            |  |  |
| Hepatobiliary disorders                         |                  |  |  |
| Bile duct obstruction                           |                  |  |  |

|   |                  |  |  |  |
|---|------------------|--|--|--|
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Bile duct stenosis                              |                  |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Cholangitis                                     |                  |  |  |  |
| subjects affected / exposed                     | 3 / 914 (0.33%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Biliary dilatation                              |                  |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |  |
| Cholecystitis                                   |                  |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Cholestasis                                     |                  |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Cholecystitis acute                             |                  |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Hepatic failure                                 |                  |  |  |  |
| subjects affected / exposed                     | 10 / 914 (1.09%) |  |  |  |
| occurrences causally related to treatment / all | 2 / 10           |  |  |  |
| deaths causally related to treatment / all      | 1 / 4            |  |  |  |
| Mixed liver injury                              |                  |  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Jaundice  |                  |  |  |
| subjects affected / exposed                     | 10 / 914 (1.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 10           |  |  |
| deaths causally related to treatment / all      | 0 / 3            |  |  |
| Portal hypertension                             |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal and urinary disorders                     |                  |  |  |
| Chronic kidney disease                          |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Acute kidney injury                             |                  |  |  |
| subjects affected / exposed                     | 4 / 914 (0.44%)  |  |  |
| occurrences causally related to treatment / all | 1 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Calculus urinary                                |                  |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haematuria                                      |                  |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hydronephrosis                                  |                  |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Nephropathy toxic                               |                  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Proteinuria                                     |                 |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%) |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal failure                                   |                 |  |  |
| subjects affected / exposed                     | 3 / 914 (0.33%) |  |  |
| occurrences causally related to treatment / all | 1 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urinary retention                               |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Arthritis reactive                              |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Back pain                                       |                 |  |  |
| subjects affected / exposed                     | 3 / 914 (0.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bone pain                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal pain                            |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Osteoarthritis                                  |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pathological fracture                           |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Abdominal sepsis                                |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Abdominal wall abscess                          |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Anal abscess                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Aspergilloma                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bacterial pyelonephritis                        |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bacterial sepsis                                |                 |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Biliary tract infection                         |                 |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Biliary sepsis                                  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Bronchitis                                      |                 |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cellulitis                                      |                 |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cellulitis gangrenous                           |                 |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Clostridium difficile colitis                   |                 |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cystitis escherichia                            |                 |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Device related infection                        |                 |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cytomegalovirus colitis                         |                 |  |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                                   | 1 / 914 (0.11%) |  |  |  |
| occurrences causally related to treatment / all               | 0 / 1           |  |  |  |
| deaths causally related to treatment / all                    | 0 / 0           |  |  |  |
| Endophthalmitis   |                 |  |  |  |
| subjects affected / exposed                                   | 1 / 914 (0.11%) |  |  |  |
| occurrences causally related to treatment / all               | 1 / 1           |  |  |  |
| deaths causally related to treatment / all                    | 0 / 0           |  |  |  |
| Escherichia pyelonephritis                                    |                 |  |  |  |
| subjects affected / exposed                                   | 1 / 914 (0.11%) |  |  |  |
| occurrences causally related to treatment / all               | 0 / 1           |  |  |  |
| deaths causally related to treatment / all                    | 0 / 0           |  |  |  |
| Escherichia sepsis  |                 |  |  |  |
| subjects affected / exposed                                   | 2 / 914 (0.22%) |  |  |  |
| occurrences causally related to treatment / all               | 1 / 3           |  |  |  |
| deaths causally related to treatment / all                    | 0 / 0           |  |  |  |
| Gastroenteritis viral   |                 |  |  |  |
| subjects affected / exposed                                   | 1 / 914 (0.11%) |  |  |  |
| occurrences causally related to treatment / all               | 0 / 1           |  |  |  |
| deaths causally related to treatment / all                    | 0 / 0           |  |  |  |
| Escherichia urinary tract infection                           |                 |  |  |  |
| subjects affected / exposed                                   | 4 / 914 (0.44%) |  |  |  |
| occurrences causally related to treatment / all               | 1 / 4           |  |  |  |
| deaths causally related to treatment / all                    | 0 / 0           |  |  |  |
| Infection   |                 |  |  |  |
| subjects affected / exposed                                   | 1 / 914 (0.11%) |  |  |  |
| occurrences causally related to treatment / all               | 1 / 1           |  |  |  |
| deaths causally related to treatment / all                    | 0 / 0           |  |  |  |
| Infective exacerbation of chronic obstructive airways disease |                 |  |  |  |
| subjects affected / exposed                                   | 1 / 914 (0.11%) |  |  |  |
| occurrences causally related to treatment / all               | 1 / 1           |  |  |  |
| deaths causally related to treatment / all                    | 0 / 0           |  |  |  |
| Listeria sepsis   |                 |  |  |  |



|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Liver abscess                                   |                 |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Lower respiratory tract infection               |                 |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Lymphangitis                                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Medical device site infection                   |                 |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Muscle abscess                                  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Neutropenic sepsis                              |                 |  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pelvic abscess                                  |                 |  |  |  |
| subjects affected / exposed                     | 4 / 914 (0.44%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Pneumonia                                       |                 |  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 21 / 914 (2.30%) |  |  |
| occurrences causally related to treatment / all | 4 / 21           |  |  |
| deaths causally related to treatment / all      | 0 / 3            |  |  |
| Pneumonia pseudomonal                           |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pneumonia staphylococcal                        |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Postoperative wound infection                   |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Psoas abscess                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pyelonephritis                                  |                  |  |  |
| subjects affected / exposed                     | 2 / 914 (0.22%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pyelonephritis acute                            |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pyopneumothorax                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Respiratory tract infection                     |                  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Sepsis  |                 |  |  |
| subjects affected / exposed                     | 5 / 914 (0.55%) |  |  |
| occurrences causally related to treatment / all | 1 / 5           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Septic shock                                    |                 |  |  |
| subjects affected / exposed                     | 4 / 914 (0.44%) |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 2           |  |  |
| Spinal cord infection                           |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Staphylococcal sepsis                           |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Stenotrophomonas sepsis                         |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Subcutaneous abscess                            |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tracheobronchitis bacterial                     |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urinary tract infection                         |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urosepsis                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urinary tract infection staphylococcal          |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vascular device infection                       |                 |  |  |
| subjects affected / exposed                     | 3 / 914 (0.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Cachexia  |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Decreased appetite                              |                 |  |  |
| subjects affected / exposed                     | 5 / 914 (0.55%) |  |  |
| occurrences causally related to treatment / all | 0 / 5           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dehydration                                     |                 |  |  |
| subjects affected / exposed                     | 8 / 914 (0.88%) |  |  |
| occurrences causally related to treatment / all | 4 / 8           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Hypocalcaemia                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypoalbuminaemia                                |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 2 / 914 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Hypokalaemia</b>                             |                 |  |  |
| subjects affected / exposed                     | 3 / 914 (0.33%) |  |  |
| occurrences causally related to treatment / all | 1 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Malnutrition</b>                             |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Steroid diabetes</b>                         |                 |  |  |
| subjects affected / exposed                     | 1 / 914 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

|   |                    |  |  |
|---|--------------------|--|--|
| <b>Non-serious adverse events</b>                     | S95005             |  |  |
| Total subjects affected by non-serious adverse events |                    |  |  |
| subjects affected / exposed                           | 839 / 914 (91.79%) |  |  |
| <b>Investigations</b>                                 |                    |  |  |
| Blood alkaline phosphatase increased                  |                    |  |  |
| subjects affected / exposed                           | 57 / 914 (6.24%)   |  |  |
| occurrences (all)                                     | 60                 |  |  |
| Gamma-glutamyltransferase increased                   |                    |  |  |
| subjects affected / exposed                           | 46 / 914 (5.03%)   |  |  |
| occurrences (all)                                     | 47                 |  |  |
| Neutrophil count decreased                            |                    |  |  |
| subjects affected / exposed                           | 58 / 914 (6.35%)   |  |  |
| occurrences (all)                                     | 96                 |  |  |
| Weight decreased                                      |                    |  |  |
| subjects affected / exposed                           | 50 / 914 (5.47%)   |  |  |
| occurrences (all)                                     | 51                 |  |  |

|   |  |  |  |
|---|--|--|--|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)<br>Malignant neoplasm progression<br>subjects affected / exposed<br>occurrences (all)   | 57 / 914 (6.24%)<br>58   |  |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Neutropenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)      | 234 / 914 (25.60%)<br>259<br><br>427 / 914 (46.72%)<br>845<br><br>65 / 914 (7.11%)<br>76 |  |  |
| General disorders and administration site conditions<br>Asthenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Pyrexia<br>subjects affected / exposed<br>occurrences (all)<br><br>Fatigue<br>subjects affected / exposed<br>occurrences (all)  | 171 / 914 (18.71%)<br>215<br><br>73 / 914 (7.99%)<br>84<br><br>165 / 914 (18.05%)<br>189 |  |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Nausea | 74 / 914 (8.10%)<br>87<br><br>92 / 914 (10.07%)<br>98<br><br>218 / 914 (23.85%)<br>290   |  |  |

|                                    |                    |  |  |
|------------------------------------|--------------------|--|--|
| subjects affected / exposed        | 268 / 914 (29.32%) |  |  |
| occurrences (all)                  | 367                |  |  |
| Vomiting                           |                    |  |  |
| subjects affected / exposed        | 152 / 914 (16.63%) |  |  |
| occurrences (all)                  | 202                |  |  |
| Metabolism and nutrition disorders |                    |  |  |
| Decreased appetite                 |                    |  |  |
| subjects affected / exposed        | 145 / 914 (15.86%) |  |  |
| occurrences (all)                  | 157                |  |  |

## 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

None reported