



## Clinical trial results:

### Multicentre, Single-Arm, Open-Label, Clinical Trial Intended to Provide Early Access to Cabazitaxel in Patients with Metastatic Hormone Refractory Prostate Cancer Previously Treated with a Docetaxel-Containing Regimen and to Document Safety of Cabazitaxel in These Patients

#### Summary

|                          |                                           |
|--------------------------|-------------------------------------------|
| EudraCT number           | 2010-021128-92                            |
| Trial protocol           | GB CZ BE DK ES IT SE FI AT PT HU IE BG SK |
| Global end of trial date | 21 December 2014                          |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 24 July 2016 |
| First version publication date | 24 July 2016 |

#### Trial information

##### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | CABAZ_C_05331 |
|-----------------------|---------------|

##### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT01254279     |
| WHO universal trial number (UTN)   | U1111-1115-2476 |

Notes:

#### Sponsors

|                              |                                                                                             |
|------------------------------|---------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Sanofi aventis recherche & développement                                                    |
| Sponsor organisation address | 1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380                                  |
| Public contact               | Trial Transparency Team,<br>Sanofi aventis recherche & développement, Contact-US@sanofi.com |
| Scientific contact           | Trial Transparency Team,<br>Sanofi aventis recherche & développement, Contact-US@sanofi.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                       | 08 December 2015 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 21 December 2014 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To allow subjects similar to those evaluated in the TROPIC trial (EFC1693) , and Investigators access to cabazitaxel for the management of metastatic Hormone Refractory Prostate Cancer (mHRPC) in subjects who had progressed during or after docetaxel, and to document the overall safety of cabazitaxel in these subjects.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 20 December 2010 |
| 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 | Poland: 5           |
| Country: Number of subjects enrolled | Portugal: 20        |
| Country: Number of subjects enrolled | Romania: 16         |
| Country: Number of subjects enrolled | Slovakia: 15        |
| Country: Number of subjects enrolled | Spain: 156          |
| Country: Number of subjects enrolled | Sweden: 8           |
| Country: Number of subjects enrolled | United Kingdom: 112 |
| Country: Number of subjects enrolled | Austria: 7          |
| Country: Number of subjects enrolled | Belgium: 45         |
| Country: Number of subjects enrolled | Bulgaria: 21        |
| Country: Number of subjects enrolled | Czech Republic: 15  |
| Country: Number of subjects enrolled | Denmark: 24         |
| Country: Number of subjects enrolled | Finland: 13         |
| Country: Number of subjects enrolled | Hungary: 18         |
| Country: Number of subjects enrolled | Ireland: 22         |
| Country: Number of subjects enrolled | Italy: 219          |

|                                      |                            |
|--------------------------------------|----------------------------|
| Country: Number of subjects enrolled | Luxembourg: 1              |
| Country: Number of subjects enrolled | Australia: 104             |
| Country: Number of subjects enrolled | Bosnia and Herzegovina: 13 |
| Country: Number of subjects enrolled | Canada: 61                 |
| Country: Number of subjects enrolled | Croatia: 6                 |
| Country: Number of subjects enrolled | India: 6                   |
| Country: Number of subjects enrolled | Kazakhstan: 13             |
| Country: Number of subjects enrolled | Malaysia: 5                |
| Country: Number of subjects enrolled | Mexico: 12                 |
| Country: Number of subjects enrolled | Philippines: 6             |
| Country: Number of subjects enrolled | Serbia: 10                 |
| Country: Number of subjects enrolled | Singapore: 5               |
| Country: Number of subjects enrolled | Taiwan: 23                 |
| Worldwide total number of subjects   | 981                        |
| EEA total number of subjects         | 723                        |

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)                      | 298 |
| From 65 to 84 years                       | 676 |
| 85 years and over                         | 7   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The study was conducted in 29 countries. A total of 981 subjects were enrolled between 20 December 2010 and 27 September 2013.

### Period 1

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

### Arms

|           |             |
|-----------|-------------|
| Arm title | Cabazitaxel |
|-----------|-------------|

Arm description:

Cabazitaxel 25 mg/m<sup>2</sup> administered on Day 1 of each 3-weeks cycle in combination with prednisone or prednisolone 10 mg daily until disease progression, death, unacceptable toxicity or Investigator's decision.

|                                        |                                       |
|----------------------------------------|---------------------------------------|
| Arm type                               | Experimental                          |
| Investigational medicinal product name | Cabazitaxel                           |
| Investigational medicinal product code | XRP6258                               |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Cabazitaxel 25 mg/m<sup>2</sup> intravenous (IV) infusion administered for one hour.

|                                        |                         |
|----------------------------------------|-------------------------|
| Investigational medicinal product name | Prednisone/Prednisolone |
| Investigational medicinal product code |                         |
| Other name                             |                         |
| Pharmaceutical forms                   | Tablet                  |
| Routes of administration               | Oral use                |

Dosage and administration details:

Prednisone or prednisolone 10 mg daily administered according to its labelling.

| Number of subjects in period 1     | Cabazitaxel        |
|------------------------------------|--------------------|
| Started                            | 981                |
| Disease Progression                | 457 <sup>[1]</sup> |
| Adverse Events                     | 254 <sup>[2]</sup> |
| Physician/Investigator's Decision  | 159 <sup>[3]</sup> |
| Cabazitaxel Commercially Available | 4 <sup>[4]</sup>   |
| Other than specified               | 107 <sup>[5]</sup> |
| Completed                          | 981                |

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Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Met EOT criteria (treatment until disease progression, death, unacceptable toxicity [AE], Investigator's decision or cabazitaxel commercially available).

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Met EOT criteria (treatment until disease progression, death, unacceptable toxicity [AE], Investigator's decision or cabazitaxel commercially available).

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Met EOT criteria (treatment until disease progression, death, unacceptable toxicity [AE], Investigator's decision or cabazitaxel commercially available).

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Met end of treatment (EOT) criteria (treatment until disease progression, death, unacceptable toxicity [AE], Investigator's decision or cabazitaxel commercially available).

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Met EOT criteria (treatment until disease progression, death, unacceptable toxicity [AE], Investigator's decision or cabazitaxel commercially available).

## Baseline characteristics

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Cabazitaxel |
|-----------------------|-------------|

Reporting group description:

Cabazitaxel 25 mg/m<sup>2</sup> administered on Day 1 of each 3-weeks cycle in combination with prednisone or prednisolone 10 mg daily until disease progression, death, unacceptable toxicity or Investigator's decision.

| Reporting group values                                                  | Cabazitaxel   | Total |  |
|-------------------------------------------------------------------------|---------------|-------|--|
| Number of subjects                                                      | 981           | 981   |  |
| Age categorical<br>Units: Subjects                                      |               |       |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 68.2<br>± 7.7 | -     |  |
| Gender categorical<br>Units: Subjects                                   |               |       |  |
| Female                                                                  | 0             | 0     |  |
| Male                                                                    | 981           | 981   |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                             |             |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| Reporting group title                                                                                                                                                                                                                                       | Cabazitaxel |
| Reporting group description:<br>Cabazitaxel 25 mg/m <sup>2</sup> administered on Day 1 of each 3-weeks cycle in combination with prednisone or prednisolone 10 mg daily until disease progression, death, unacceptable toxicity or Investigator's decision. |             |

### Primary: Number of Subjects with Early Access to Cabazitaxel

|                                                                                                                                                                       |                                                                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|
| End point title                                                                                                                                                       | Number of Subjects with Early Access to Cabazitaxel <sup>[1]</sup> |
| End point description:<br>Safety population included the subjects who had signed the informed consent form and had received at least part of one dose of cabazitaxel. |                                                                    |
| End point type                                                                                                                                                        | Primary                                                            |
| End point timeframe:<br>From enrollment up to 30 days after the last administration of study drug (205 weeks + 30 days).                                              |                                                                    |

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: As the endpoint is descriptive in nature, no statistical analysis is provided.

| End point values            | Cabazitaxel     |  |  |  |
|-----------------------------|-----------------|--|--|--|
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 981             |  |  |  |
| Units: Subjects             |                 |  |  |  |
| number (not applicable)     | 981             |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects with Treatment-Emergent Adverse Events (TEAE)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Percentage of Subjects with Treatment-Emergent Adverse Events (TEAE) |
| End point description:<br>An Adverse Event (AE) was defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which did not necessarily had a causal relationship with this treatment. AEs that occurred or worsened after the first day of dosing upto 30 days after the last administration of Cabazitaxel, were considered as treatment-emergent adverse events (TEAE). A serious adverse event (SAE) was defined as any untoward medical occurrence that at any dose resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. Any TEAE included subjects with both serious and non-serious AEs. Analysis was performed on safety population. |                                                                      |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Secondary                                                            |
| End point timeframe:<br>From enrollment upto 30 days after the last administration of study drug (205 weeks + 30 days)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                      |

|                                               |                 |  |  |  |
|-----------------------------------------------|-----------------|--|--|--|
| <b>End point values</b>                       | Cabazitaxel     |  |  |  |
| Subject group type                            | Reporting group |  |  |  |
| Number of subjects analysed                   | 981             |  |  |  |
| Units: Percentage of Subjects                 |                 |  |  |  |
| number (not applicable)                       |                 |  |  |  |
| Any TEAE                                      | 95.2            |  |  |  |
| Any possibly related TEAE                     | 86.2            |  |  |  |
| Any serious TEAE                              | 40.8            |  |  |  |
| Any TEAE leading to death                     | 6.6             |  |  |  |
| Any TEAE leading to treatment discontinuation | 25.8            |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (205 weeks + 30 days) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events and death are treatment-emergent adverse events that is AEs that developed/worsened and death that occurred during the 'on treatment period' (the period from the first administration of study drug up to 30 days after the last administration of study drug).

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 15.0 |
|--------------------|------|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Cabazitaxel |
|-----------------------|-------------|

Reporting group description:

Cabazitaxel 25 mg/m<sup>2</sup> administered on Day 1 of each 3-weeks cycle in combination with prednisone or prednisolone 10 mg daily until disease progression, death, unacceptable toxicity or Investigator's decision.

| Serious adverse events                                              | Cabazitaxel        |  |  |
|---------------------------------------------------------------------|--------------------|--|--|
| Total subjects affected by serious adverse events                   |                    |  |  |
| subjects affected / exposed                                         | 400 / 981 (40.77%) |  |  |
| number of deaths (all causes)                                       | 216                |  |  |
| number of deaths resulting from adverse events                      |                    |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |  |  |
| Bladder Cancer                                                      |                    |  |  |
| subjects affected / exposed                                         | 1 / 981 (0.10%)    |  |  |
| occurrences causally related to treatment / all                     | 0 / 1              |  |  |
| deaths causally related to treatment / all                          | 0 / 0              |  |  |
| Brain Neoplasm Malignant                                            |                    |  |  |
| subjects affected / exposed                                         | 1 / 981 (0.10%)    |  |  |
| occurrences causally related to treatment / all                     | 0 / 1              |  |  |
| deaths causally related to treatment / all                          | 0 / 0              |  |  |
| Metastases To Central Nervous System                                |                    |  |  |
| subjects affected / exposed                                         | 1 / 981 (0.10%)    |  |  |
| occurrences causally related to treatment / all                     | 0 / 1              |  |  |
| deaths causally related to treatment / all                          | 0 / 0              |  |  |
| Metastases To Lung                                                  |                    |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metastases To Spine                             |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metastatic Pain                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vascular disorders                              |                 |  |  |
| Circulatory Collapse                            |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Deep Vein Thrombosis                            |                 |  |  |
| subjects affected / exposed                     | 6 / 981 (0.61%) |  |  |
| occurrences causally related to treatment / all | 0 / 8           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Embolism Venous                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haematoma                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypovolaemic Shock                              |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lymphoedema                                     |                 |  |  |

|                                                      |                 |  |  |
|------------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                          | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all      | 6 / 6           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Orthostatic Hypotension                              |                 |  |  |
| subjects affected / exposed                          | 2 / 981 (0.20%) |  |  |
| occurrences causally related to treatment / all      | 1 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Venous Thrombosis                                    |                 |  |  |
| subjects affected / exposed                          | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all      | 0 / 8           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Venous Thrombosis Limb                               |                 |  |  |
| subjects affected / exposed                          | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Surgical and medical procedures                      |                 |  |  |
| Medical Device Change                                |                 |  |  |
| subjects affected / exposed                          | 1 / 981 (0.10%) |  |  |
| 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                          | 6 / 981 (0.61%) |  |  |
| occurrences causally related to treatment / all      | 5 / 7           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Chest Pain                                           |                 |  |  |
| subjects affected / exposed                          | 3 / 981 (0.31%) |  |  |
| occurrences causally related to treatment / all      | 1 / 3           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Death                                                |                 |  |  |
| subjects affected / exposed                          | 2 / 981 (0.20%) |  |  |
| occurrences causally related to treatment / all      | 2 / 2           |  |  |
| deaths causally related to treatment / all           | 2 / 2           |  |  |

|                                                 |                  |  |  |  |
|-------------------------------------------------|------------------|--|--|--|
| Device Occlusion                                |                  |  |  |  |
| subjects affected / exposed                     | 5 / 981 (0.51%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Disease Progression                             |                  |  |  |  |
| subjects affected / exposed                     | 20 / 981 (2.04%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 22           |  |  |  |
| deaths causally related to treatment / all      | 0 / 15           |  |  |  |
| Fatigue                                         |                  |  |  |  |
| subjects affected / exposed                     | 8 / 981 (0.82%)  |  |  |  |
| occurrences causally related to treatment / all | 15 / 15          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| General Physical Health Deterioration           |                  |  |  |  |
| subjects affected / exposed                     | 9 / 981 (0.92%)  |  |  |  |
| occurrences causally related to treatment / all | 4 / 9            |  |  |  |
| deaths causally related to treatment / all      | 1 / 3            |  |  |  |
| Influenza Like Illness                          |                  |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Malaise                                         |                  |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Multi-Organ Failure                             |                  |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Oedema Peripheral                               |                  |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Pain                                            |                  |  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 2 / 981 (0.20%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pyrexia                                         |                  |  |  |
| subjects affected / exposed                     | 16 / 981 (1.63%) |  |  |
| occurrences causally related to treatment / all | 5 / 16           |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Immune system disorders                         |                  |  |  |
| Drug Hypersensitivity                           |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypersensitivity                                |                  |  |  |
| subjects affected / exposed                     | 3 / 981 (0.31%)  |  |  |
| occurrences causally related to treatment / all | 3 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Reproductive system and breast disorders        |                  |  |  |
| Pelvic Pain                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Scrotal Ulcer                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Respiratory, thoracic and mediastinal disorders |                  |  |  |
| Acute Respiratory Failure                       |                  |  |  |
| subjects affected / exposed                     | 2 / 981 (0.20%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 1 / 2            |  |  |
| Dyspnoea                                        |                  |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| subjects affected / exposed                     | 7 / 981 (0.71%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 9           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Epistaxis                                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pleural Effusion                                |                 |  |  |  |
| subjects affected / exposed                     | 2 / 981 (0.20%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumonitis                                     |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumothorax                                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pulmonary Artery Thrombosis                     |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pulmonary Embolism                              |                 |  |  |  |
| subjects affected / exposed                     | 7 / 981 (0.71%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 7           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Pulmonary Microemboli                           |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pulmonary Oedema                                |                 |  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 1 / 1           |  |  |
| Respiratory Failure                             |                 |  |  |
| subjects affected / exposed                     | 2 / 981 (0.20%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Psychiatric disorders                           |                 |  |  |
| Confusional State                               |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Investigations                                  |                 |  |  |
| Haemoglobin Decreased                           |                 |  |  |
| subjects affected / exposed                     | 6 / 981 (0.61%) |  |  |
| occurrences causally related to treatment / all | 6 / 8           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Neutrophil Count Decreased                      |                 |  |  |
| subjects affected / exposed                     | 3 / 981 (0.31%) |  |  |
| occurrences causally related to treatment / all | 3 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Platelet Count Decreased                        |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| White Blood Cell Count Decreased                |                 |  |  |
| subjects affected / exposed                     | 2 / 981 (0.20%) |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| Cystitis Radiation                              |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| Fall                                            |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Femur Fracture                                  |                 |  |  |  |
| subjects affected / exposed                     | 3 / 981 (0.31%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Humerus Fracture                                |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Infusion Related Reaction                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Ligament Injury                                 |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Ligament Rupture                                |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Spinal Compression Fracture                     |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Spinal Cord Injury Cauda Equina                 |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Traumatic Fracture                              |                 |  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Angina Pectoris                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atrial Fibrillation                             |                 |  |  |
| subjects affected / exposed                     | 4 / 981 (0.41%) |  |  |
| occurrences causally related to treatment / all | 2 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atrial Tachycardia                              |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac Disorder                                |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Cardiac Failure                                 |                 |  |  |
| subjects affected / exposed                     | 3 / 981 (0.31%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac Failure Congestive                      |                 |  |  |
| subjects affected / exposed                     | 2 / 981 (0.20%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardio-Respiratory Arrest                       |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 1 / 1           |  |  |
| Cardiogenic Shock                               |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Cardiopulmonary Failure                         |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Left Ventricular Dysfunction                    |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Myocardial Infarction                           |                 |  |  |
| subjects affected / exposed                     | 3 / 981 (0.31%) |  |  |
| occurrences causally related to treatment / all | 1 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Supraventricular Tachycardia                    |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nervous system disorders                        |                 |  |  |
| Aphasia                                         |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cerebral Haemorrhage                            |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cerebral Ischaemia                              |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cerebrovascular Accident                        |                 |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| subjects affected / exposed                     | 2 / 981 (0.20%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Dizziness                                       |                 |  |  |  |
| subjects affected / exposed                     | 2 / 981 (0.20%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Hepatic Encephalopathy                          |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Loss Of Consciousness                           |                 |  |  |  |
| subjects affected / exposed                     | 2 / 981 (0.20%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Nerve Root Compression                          |                 |  |  |  |
| subjects affected / exposed                     | 3 / 981 (0.31%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Paraesthesia                                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Paraplegia                                      |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Paresis                                         |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Presyncope                                      |                 |  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Spinal Cord Compression                         |                  |  |  |
| subjects affected / exposed                     | 11 / 981 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 17           |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Blood and lymphatic system disorders            |                  |  |  |
| Agranulocytosis                                 |                  |  |  |
| subjects affected / exposed                     | 4 / 981 (0.41%)  |  |  |
| occurrences causally related to treatment / all | 4 / 4            |  |  |
| deaths causally related to treatment / all      | 1 / 1            |  |  |
| Anaemia                                         |                  |  |  |
| subjects affected / exposed                     | 12 / 981 (1.22%) |  |  |
| occurrences causally related to treatment / all | 19 / 22          |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Disseminated Intravascular Coagulation          |                  |  |  |
| subjects affected / exposed                     | 2 / 981 (0.20%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Febrile Neutropenia                             |                  |  |  |
| subjects affected / exposed                     | 52 / 981 (5.30%) |  |  |
| occurrences causally related to treatment / all | 58 / 58          |  |  |
| deaths causally related to treatment / all      | 2 / 2            |  |  |
| Granulocytopenia                                |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haemorrhagic Anaemia                            |                  |  |  |
| subjects affected / exposed                     | 2 / 981 (0.20%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Leukopenia                                      |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 7 / 981 (0.71%)  |  |  |
| occurrences causally related to treatment / all | 7 / 7            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Neutropenia                                     |                  |  |  |
| subjects affected / exposed                     | 24 / 981 (2.45%) |  |  |
| occurrences causally related to treatment / all | 24 / 25          |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pancytopenia                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 1 / 1            |  |  |
| Thrombocytopenia                                |                  |  |  |
| subjects affected / exposed                     | 4 / 981 (0.41%)  |  |  |
| occurrences causally related to treatment / all | 3 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastrointestinal disorders                      |                  |  |  |
| Abdominal Discomfort                            |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Abdominal Distension                            |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Abdominal Pain                                  |                  |  |  |
| subjects affected / exposed                     | 6 / 981 (0.61%)  |  |  |
| occurrences causally related to treatment / all | 3 / 7            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Abdominal Pain Lower                            |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Colitis                                         |                  |  |  |

|                                                 |                  |  |  |  |
|-------------------------------------------------|------------------|--|--|--|
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Constipation                                    |                  |  |  |  |
| subjects affected / exposed                     | 5 / 981 (0.51%)  |  |  |  |
| occurrences causally related to treatment / all | 3 / 7            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Diarrhoea                                       |                  |  |  |  |
| subjects affected / exposed                     | 25 / 981 (2.55%) |  |  |  |
| occurrences causally related to treatment / all | 26 / 28          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Duodenal Perforation                            |                  |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Duodenal Ulcer                                  |                  |  |  |  |
| subjects affected / exposed                     | 3 / 981 (0.31%)  |  |  |  |
| occurrences causally related to treatment / all | 3 / 3            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Dyspepsia                                       |                  |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Enterovesical Fistula                           |                  |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Faecal Incontinence                             |                  |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Gastric Ulcer                                   |                  |  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastric Ulcer Haemorrhage                       |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 1 / 1           |  |  |
| Gastrointestinal Haemorrhage                    |                 |  |  |
| subjects affected / exposed                     | 2 / 981 (0.20%) |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |
| deaths causally related to treatment / all      | 1 / 1           |  |  |
| Intestinal Obstruction                          |                 |  |  |
| subjects affected / exposed                     | 3 / 981 (0.31%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Large Intestine Perforation                     |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 1 / 1           |  |  |
| Nausea                                          |                 |  |  |
| subjects affected / exposed                     | 9 / 981 (0.92%) |  |  |
| occurrences causally related to treatment / all | 9 / 10          |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Neutropenic Colitis                             |                 |  |  |
| subjects affected / exposed                     | 2 / 981 (0.20%) |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |
| deaths causally related to treatment / all      | 1 / 1           |  |  |
| Pancreatitis Acute                              |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Proctitis                                       |                 |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Rectal Haemorrhage                              |                  |  |  |
| subjects affected / exposed                     | 2 / 981 (0.20%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Retching                                        |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Small Intestinal Obstruction                    |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Upper Gastrointestinal Haemorrhage              |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vomiting                                        |                  |  |  |
| subjects affected / exposed                     | 12 / 981 (1.22%) |  |  |
| occurrences causally related to treatment / all | 10 / 14          |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hepatobiliary disorders                         |                  |  |  |
| Cholelithiasis                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hepatic Failure                                 |                  |  |  |
| subjects affected / exposed                     | 4 / 981 (0.41%)  |  |  |
| occurrences causally related to treatment / all | 1 / 4            |  |  |
| deaths causally related to treatment / all      | 1 / 3            |  |  |
| Hepatic Function Abnormal                       |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hepatotoxicity                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal and urinary disorders                     |                  |  |  |
| Anuria                                          |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Bladder Neck Obstruction                        |                  |  |  |
| subjects affected / exposed                     | 2 / 981 (0.20%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Bladder Perforation                             |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cystitis Haemorrhagic                           |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haematuria                                      |                  |  |  |
| subjects affected / exposed                     | 33 / 981 (3.36%) |  |  |
| occurrences causally related to treatment / all | 5 / 48           |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Haemorrhage Urinary Tract                       |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hydronephrosis                                  |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 5 / 981 (0.51%)  |  |  |
| occurrences causally related to treatment / all | 0 / 13           |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Oliguria                                        |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pollakiuria                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal Failure                                   |                  |  |  |
| subjects affected / exposed                     | 4 / 981 (0.41%)  |  |  |
| occurrences causally related to treatment / all | 1 / 4            |  |  |
| deaths causally related to treatment / all      | 1 / 3            |  |  |
| Renal Failure Acute                             |                  |  |  |
| subjects affected / exposed                     | 12 / 981 (1.22%) |  |  |
| occurrences causally related to treatment / all | 5 / 12           |  |  |
| deaths causally related to treatment / all      | 2 / 3            |  |  |
| Renal Impairment                                |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal Pain                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal Tubular Necrosis                          |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Urinary Retention                               |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 10 / 981 (1.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 14           |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Urinary Tract Obstruction                       |                  |  |  |
| subjects affected / exposed                     | 4 / 981 (0.41%)  |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Urogenital Haemorrhage                          |                  |  |  |
| subjects affected / exposed                     | 2 / 981 (0.20%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Musculoskeletal and connective tissue disorders |                  |  |  |
| Arthralgia                                      |                  |  |  |
| subjects affected / exposed                     | 3 / 981 (0.31%)  |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Back Pain                                       |                  |  |  |
| subjects affected / exposed                     | 13 / 981 (1.33%) |  |  |
| occurrences causally related to treatment / all | 1 / 17           |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Bone Pain                                       |                  |  |  |
| subjects affected / exposed                     | 7 / 981 (0.71%)  |  |  |
| occurrences causally related to treatment / all | 0 / 10           |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Flank Pain                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Muscular Weakness                               |                  |  |  |
| subjects affected / exposed                     | 2 / 981 (0.20%)  |  |  |
| occurrences causally related to treatment / all | 2 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Musculoskeletal Pain                            |                  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Osteonecrosis Of Jaw                            |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pain In Extremity                               |                 |  |  |
| subjects affected / exposed                     | 4 / 981 (0.41%) |  |  |
| occurrences causally related to treatment / all | 0 / 11          |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Pain In Jaw                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pathological Fracture                           |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Spinal Column Stenosis                          |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| 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 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 1 / 1           |  |  |
| Abscess Limb                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bacterial Sepsis                                |                 |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| subjects affected / exposed                     | 2 / 981 (0.20%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Bronchopneumonia                                |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Campylobacter Infection                         |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Candidiasis                                     |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cellulitis                                      |                 |  |  |  |
| subjects affected / exposed                     | 3 / 981 (0.31%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 4           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Clostridial Infection                           |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Clostridium Difficile Colitis                   |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cystitis                                        |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Device Related Infection                        |                 |  |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Enterococcal Bacteraemia                        |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Erysipelas                                      |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gastroenteritis                                 |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Haemophilus Infection                           |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Herpes Zoster                                   |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Infection                                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Infectious Peritonitis                          |                 |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Lobar Pneumonia                                 |                 |  |  |  |

|                                                 |                  |  |  |  |
|-------------------------------------------------|------------------|--|--|--|
| subjects affected / exposed                     | 2 / 981 (0.20%)  |  |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Lower Respiratory Tract Infection               |                  |  |  |  |
| subjects affected / exposed                     | 8 / 981 (0.82%)  |  |  |  |
| occurrences causally related to treatment / all | 3 / 11           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Lung Infection                                  |                  |  |  |  |
| subjects affected / exposed                     | 3 / 981 (0.31%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |  |
| Necrotising Fasciitis                           |                  |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Neutropenic Infection                           |                  |  |  |  |
| subjects affected / exposed                     | 8 / 981 (0.82%)  |  |  |  |
| occurrences causally related to treatment / all | 10 / 10          |  |  |  |
| deaths causally related to treatment / all      | 2 / 2            |  |  |  |
| Neutropenic Sepsis                              |                  |  |  |  |
| subjects affected / exposed                     | 20 / 981 (2.04%) |  |  |  |
| occurrences causally related to treatment / all | 20 / 20          |  |  |  |
| deaths causally related to treatment / all      | 1 / 1            |  |  |  |
| Otitis Media                                    |                  |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Pelvic Abscess                                  |                  |  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Peritonitis                                     |                  |  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 1 / 1            |  |  |
| Pneumonia                                       |                  |  |  |
| subjects affected / exposed                     | 16 / 981 (1.63%) |  |  |
| occurrences causally related to treatment / all | 14 / 21          |  |  |
| deaths causally related to treatment / all      | 3 / 3            |  |  |
| Pneumonia Viral                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pseudomembranous Colitis                        |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 1 / 1            |  |  |
| Pseudomonas Infection                           |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pyelonephritis                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Respiratory Tract Infection                     |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Sepsis                                          |                  |  |  |
| subjects affected / exposed                     | 14 / 981 (1.43%) |  |  |
| occurrences causally related to treatment / all | 10 / 16          |  |  |
| deaths causally related to treatment / all      | 1 / 2            |  |  |
| Septic Shock                                    |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 6 / 981 (0.61%)  |  |  |
| occurrences causally related to treatment / all | 5 / 6            |  |  |
| deaths causally related to treatment / all      | 2 / 2            |  |  |
| Urethritis                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 2 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Urinary Tract Infection                         |                  |  |  |
| subjects affected / exposed                     | 20 / 981 (2.04%) |  |  |
| occurrences causally related to treatment / all | 5 / 28           |  |  |
| deaths causally related to treatment / all      | 2 / 3            |  |  |
| Urosepsis                                       |                  |  |  |
| subjects affected / exposed                     | 6 / 981 (0.61%)  |  |  |
| occurrences causally related to treatment / all | 2 / 7            |  |  |
| deaths causally related to treatment / all      | 0 / 2            |  |  |
| Metabolism and nutrition disorders              |                  |  |  |
| Cachexia                                        |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Decreased Appetite                              |                  |  |  |
| subjects affected / exposed                     | 2 / 981 (0.20%)  |  |  |
| occurrences causally related to treatment / all | 3 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Dehydration                                     |                  |  |  |
| subjects affected / exposed                     | 8 / 981 (0.82%)  |  |  |
| occurrences causally related to treatment / all | 6 / 8            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Diabetic Ketoacidosis                           |                  |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 1 / 1            |  |  |
| Gout                                            |                  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hyperglycaemia                                  |                 |  |  |
| subjects affected / exposed                     | 2 / 981 (0.20%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hyperkalaemia                                   |                 |  |  |
| subjects affected / exposed                     | 2 / 981 (0.20%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypocalcaemia                                   |                 |  |  |
| subjects affected / exposed                     | 2 / 981 (0.20%) |  |  |
| occurrences causally related to treatment / all | 2 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypoglycaemia                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypokalaemia                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 981 (0.10%) |  |  |
| 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 %

| Non-serious adverse events                            | Cabazitaxel        |  |  |
|-------------------------------------------------------|--------------------|--|--|
| Total subjects affected by non-serious adverse events |                    |  |  |
| subjects affected / exposed                           | 851 / 981 (86.75%) |  |  |
| Nervous system disorders                              |                    |  |  |
| Dysgeusia                                             |                    |  |  |
| subjects affected / exposed                           | 100 / 981 (10.19%) |  |  |
| occurrences (all)                                     | 265                |  |  |
| Neuropathy Peripheral                                 |                    |  |  |

|                                                      |                    |  |  |
|------------------------------------------------------|--------------------|--|--|
| subjects affected / exposed                          | 64 / 981 (6.52%)   |  |  |
| occurrences (all)                                    | 117                |  |  |
| Blood and lymphatic system disorders                 |                    |  |  |
| Anaemia                                              |                    |  |  |
| subjects affected / exposed                          | 284 / 981 (28.95%) |  |  |
| occurrences (all)                                    | 864                |  |  |
| Leukopenia                                           |                    |  |  |
| subjects affected / exposed                          | 90 / 981 (9.17%)   |  |  |
| occurrences (all)                                    | 142                |  |  |
| Neutropenia                                          |                    |  |  |
| subjects affected / exposed                          | 216 / 981 (22.02%) |  |  |
| occurrences (all)                                    | 368                |  |  |
| General disorders and administration site conditions |                    |  |  |
| Asthenia                                             |                    |  |  |
| subjects affected / exposed                          | 224 / 981 (22.83%) |  |  |
| occurrences (all)                                    | 634                |  |  |
| Fatigue                                              |                    |  |  |
| subjects affected / exposed                          | 299 / 981 (30.48%) |  |  |
| occurrences (all)                                    | 1018               |  |  |
| Oedema Peripheral                                    |                    |  |  |
| subjects affected / exposed                          | 64 / 981 (6.52%)   |  |  |
| occurrences (all)                                    | 130                |  |  |
| Pyrexia                                              |                    |  |  |
| subjects affected / exposed                          | 75 / 981 (7.65%)   |  |  |
| occurrences (all)                                    | 87                 |  |  |
| Gastrointestinal disorders                           |                    |  |  |
| Abdominal Pain                                       |                    |  |  |
| subjects affected / exposed                          | 57 / 981 (5.81%)   |  |  |
| occurrences (all)                                    | 88                 |  |  |
| Constipation                                         |                    |  |  |
| subjects affected / exposed                          | 175 / 981 (17.84%) |  |  |
| occurrences (all)                                    | 364                |  |  |
| Diarrhoea                                            |                    |  |  |
| subjects affected / exposed                          | 393 / 981 (40.06%) |  |  |
| occurrences (all)                                    | 884                |  |  |
| Nausea                                               |                    |  |  |

|                                                 |                    |  |  |
|-------------------------------------------------|--------------------|--|--|
| subjects affected / exposed                     | 273 / 981 (27.83%) |  |  |
| occurrences (all)                               | 622                |  |  |
| Stomatitis                                      |                    |  |  |
| subjects affected / exposed                     | 67 / 981 (6.83%)   |  |  |
| occurrences (all)                               | 108                |  |  |
| Vomiting                                        |                    |  |  |
| subjects affected / exposed                     | 184 / 981 (18.76%) |  |  |
| occurrences (all)                               | 268                |  |  |
| Respiratory, thoracic and mediastinal disorders |                    |  |  |
| Cough                                           |                    |  |  |
| subjects affected / exposed                     | 59 / 981 (6.01%)   |  |  |
| occurrences (all)                               | 97                 |  |  |
| Dyspnoea                                        |                    |  |  |
| subjects affected / exposed                     | 56 / 981 (5.71%)   |  |  |
| occurrences (all)                               | 106                |  |  |
| Renal and urinary disorders                     |                    |  |  |
| Haematuria                                      |                    |  |  |
| subjects affected / exposed                     | 129 / 981 (13.15%) |  |  |
| occurrences (all)                               | 248                |  |  |
| Musculoskeletal and connective tissue disorders |                    |  |  |
| Arthralgia                                      |                    |  |  |
| subjects affected / exposed                     | 78 / 981 (7.95%)   |  |  |
| occurrences (all)                               | 155                |  |  |
| Back Pain                                       |                    |  |  |
| subjects affected / exposed                     | 121 / 981 (12.33%) |  |  |
| occurrences (all)                               | 289                |  |  |
| Bone Pain                                       |                    |  |  |
| subjects affected / exposed                     | 81 / 981 (8.26%)   |  |  |
| occurrences (all)                               | 167                |  |  |
| Pain In Extremity                               |                    |  |  |
| subjects affected / exposed                     | 64 / 981 (6.52%)   |  |  |
| occurrences (all)                               | 115                |  |  |
| Infections and infestations                     |                    |  |  |
| Urinary Tract Infection                         |                    |  |  |
| subjects affected / exposed                     | 70 / 981 (7.14%)   |  |  |
| occurrences (all)                               | 113                |  |  |

|                                                                                                              |                           |  |  |
|--------------------------------------------------------------------------------------------------------------|---------------------------|--|--|
| Metabolism and nutrition disorders<br>Decreased Appetite<br>subjects affected / exposed<br>occurrences (all) | 192 / 981 (19.57%)<br>464 |  |  |
|--------------------------------------------------------------------------------------------------------------|---------------------------|--|--|

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 29 September 2010 | It included the following changes: <ul style="list-style-type: none"><li>- Title and objectives were modified in order to emphasize the objective safety.</li><li>- Recruitment objectives (number of sites and subjects) were increased.</li><li>- The treatment duration was harmonized throughout the protocol's sections.</li><li>- The definition of Adverse Events collection period was harmonized.</li></ul>                                                                                |
| 09 February 2011  | It included the following changes: <ul style="list-style-type: none"><li>- Exclusion criteria was clarified.</li><li>- The dosing regimen was clarified.</li><li>- The use of concomitant treatment was clarified.</li><li>- The data collection was clarified.</li></ul>                                                                                                                                                                                                                           |
| 27 June 2011      | It included the following changes: <ul style="list-style-type: none"><li>- Duration of treatment was prolonged if clinical benefit and no toxicity.</li><li>- Chemotherapy delay/reduction was clarified.</li><li>- Neutropenia management: data collection addition of the use of Granulocyte Colony-Stimulating Factor (G-CSF).</li><li>- SAEs reporting was corrected.</li><li>- Hematological toxicities reporting was clarified.</li><li>- The Interim analysis section was updated.</li></ul> |
| 22 December 2011  | It included the following changes: <ul style="list-style-type: none"><li>- Exclusion criteria was clarified.</li><li>- The information on preparation and administration of cabazitaxel, and storage of the premix and infusion solution was updated.</li></ul>                                                                                                                                                                                                                                     |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported