



## Clinical trial results:

### A Study to Determine the Activity of Robatumumab (SCH 717454) in Participants With Osteosarcoma or Ewing's Sarcoma That Has Relapsed After Standard Systemic Therapy

#### Summary

|                          |                                  |
|--------------------------|----------------------------------|
| EudraCT number           | 2007-005341-38                   |
| Trial protocol           | DE FR ES SE NO NL IT CZ PT HU GB |
| Global end of trial date | 31 August 2013                   |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1            |
| This version publication date  | 16 March 2016 |
| First version publication date | 13 June 2015  |

#### Trial information

##### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | P04720 |
|-----------------------|--------|

##### Additional study identifiers

|                                    |                                 |
|------------------------------------|---------------------------------|
| ISRCTN number                      | -                               |
| ClinicalTrials.gov id (NCT number) | NCT00617890                     |
| WHO universal trial number (UTN)   | -                               |
| Other trial identifiers            | MK-7454-002: Merck study number |

Notes:

##### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Merck Sharp & Dohme Corp.  |
| Sponsor organisation address | 2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033                               |
| Public contact               | Clinical Trials Disclosure, Merck Sharp & Dohme Corp.,<br>ClinicalTrialsDisclosure@merck.com |
| Scientific contact           | Clinical Trials Disclosure, Merck Sharp & Dohme Corp.,<br>ClinicalTrialsDisclosure@merck.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                       | 31 August 2013 |
| Is this the analysis of the primary completion data? | Yes            |
| Primary completion date                              | 31 August 2011 |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 31 August 2013 |
| Was the trial ended prematurely?                     | Yes            |

Notes:

## General information about the trial

Main objective of the trial:

Group 1 -To determine tumor cell proliferation response after dosing with SCH 717454 in Subjects with resectable osteosarcoma that has relapsed after standard systemic therapy compared to the subjects historical tumor cell proliferation. Group 2 -To determine the World Health Organization (WHO) and Response Evaluation Criteria in Solid Tumors (RECIST)-defined radiological response rate to SCH 717454 in subjects with unresectable osteosarcoma refractory to standard therapy. Group 3 -To determine the WHO and RECIST-defined radiological response rate to SCH 717454 in subjects with Ewings sarcoma refractory to standard therapy.

The study was prematurely terminated for strategic reasons, not for a safety concern; analyses of a number of efficacy endpoints were not performed due to large number of incomplete or uncleaned data which occurred as a result of the early termination. All participants could continue on drug per usual standard of care as long as receiving clinical benefit per I

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statues and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 01 February 2008 |
| 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 | Netherlands: 5    |
| Country: Number of subjects enrolled | Norway: 3         |
| Country: Number of subjects enrolled | Spain: 3          |
| Country: Number of subjects enrolled | Sweden: 2         |
| Country: Number of subjects enrolled | United Kingdom: 3 |
| Country: Number of subjects enrolled | France: 22        |
| Country: Number of subjects enrolled | Germany: 12       |
| Country: Number of subjects enrolled | Hungary: 4        |
| Country: Number of subjects enrolled | Italy: 3          |
| Country: Number of subjects enrolled | Brazil: 10        |
| Country: Number of subjects enrolled | Canada: 8         |
| Country: Number of subjects enrolled | Chile: 4          |
| Country: Number of subjects enrolled | Mexico: 2         |

|                                      |                       |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Peru: 3               |
| Country: Number of subjects enrolled | Taiwan: 12            |
| Country: Number of subjects enrolled | Turkey: 1             |
| Country: Number of subjects enrolled | United States: 115    |
| Country: Number of subjects enrolled | Argentina: 1          |
| Country: Number of subjects enrolled | Australia: 1          |
| Country: Number of subjects enrolled | Guatemala: 2          |
| Country: Number of subjects enrolled | Korea, Republic of: 3 |
| Worldwide total number of subjects   | 219                   |
| EEA total number of subjects         | 57                    |

Notes:

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### Subjects enrolled per age group

|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 14  |
| Adolescents (12-17 years)                 | 56  |
| Adults (18-64 years)                      | 147 |
| From 65 to 84 years                       | 2   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

This study enrolled both adult and child participants with relapsed resectable osteosarcoma after definitive treatment, participants with relapsed unresectable osteosarcoma refractory to prior chemotherapy, and participants with Ewing sarcoma refractory to prior treatment.

### Pre-assignment

Screening details:

Participants were to have a minimum life expectancy of  $\geq 8$  weeks.

### Period 1

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

Blinding implementation details:

Group 1 participants were given randomized assignment to a dose of .3 mg/kg or 10 mg/kg of robatumumab; Group 1 was blinded (investigator and participant) but not controlled.

### Arms

|                              |                    |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes                |
| <b>Arm title</b>             | Group 1: 0.3 mg/kg |

Arm description:

Participants received robatumumab 0.3 mg/kg intravenously (IV) as a single dose on Day 1, followed by surgery on Day 10 to 14, and four week later, resumption of robatumumab 0.3 mg/kg on the same calendar day ( $\pm 3$  days) once every 2 weeks until disease recurrence or up to 1 year of dosing. This group comprised participants with resectable osteosarcoma that relapsed within 6 months of prior definitive treatment (eg surgical metastasectomy) and having at least one prior chemotherapy regimen containing a platinum agent and doxorubicin.

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

Dosage and administration details:

Robatumumab was supplied as a concentrated solution for infusion.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Group 1: 10 mg/kg |
|------------------|-------------------|

Arm description:

Participants who received robatumumab 10 mg/kg IV as a single dose on Day 1, followed by surgery on Day 10 to 14, and four week later, resumption of robatumumab 10 mg/kg on the same calendar day ( $\pm 3$  days) once every 2 weeks until disease recurrence or up to 1 year of dosing. This group comprised participants with resectable osteosarcoma that relapsed within 6 months of prior definitive treatment (eg surgical metastasectomy) and having at least one prior chemotherapy regimen containing a platinum agent and doxorubicin.

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

Dosage and administration details:

Robatumumab was supplied as a concentrated solution for infusion.

|  |  |
|--|--|
| <b>Arm title</b>   | Group 2: 10 mg/kg                      |
| Arm description:   |  |
| Participants received robatumumab 10 mg/kg IV biweekly until disease recurrence or up to 1 year of dosing. This group comprised participants with relapsed and unresectable osteosarcoma refractory to prior chemotherapy with a platinum- and doxorubicin-containing regimen. |  |
| Arm type   | Experimental                           |
| Investigational medicinal product name   | robatumumab                            |
| Investigational medicinal product code   |  |
| Other name   |  |
| Pharmaceutical forms   | Concentrate for solution for injection |
| Routes of administration   | Intravenous use                        |

Dosage and administration details:

Robatumumab was supplied as a concentrated solution for infusion.

|  |  |
|--|--|
| <b>Arm title</b>   | Group 3: 10 mg/kg                      |
| Arm description:   |  |
| Participants received robatumumab 10 mg/kg IV biweekly until disease recurrence or up to 1 year of dosing. This group comprised participants with Ewing sarcoma refractory to prior treatment with at least 3 of the following agents: ifosfamide, etoposide, cyclophosphamide, doxorubicin, or vincristine. |  |
| Arm type   | Experimental                           |
| Investigational medicinal product name   | robatumumab                            |
| Investigational medicinal product code   |  |
| Other name   |  |
| Pharmaceutical forms   | Concentrate for solution for injection |
| Routes of administration   | Intravenous use                        |

Dosage and administration details:

Robatumumab was supplied as a concentrated solution for infusion.

| <b>Number of subjects in period 1</b> | Group 1: 0.3 mg/kg | Group 1: 10 mg/kg | Group 2: 10 mg/kg |
|---------------------------------------|--------------------|-------------------|-------------------|
| Started                               | 35                 | 33                | 35                |
| Received treatment                    | 34                 | 33                | 34                |
| Completed                             | 4                  | 5                 | 0                 |
| Not completed                         | 31                 | 28                | 35                |
| Consent withdrawn by subject          | 4                  | 1                 | -                 |
| Treatment ongoing at data cut-off     | -                  | -                 | -                 |
| Adverse event, non-fatal              | 1                  | -                 | 3                 |
| Lost to follow-up                     | -                  | -                 | 1                 |
| Lack of efficacy                      | 23                 | 26                | 30                |
| Protocol deviation                    | 2                  | 1                 | -                 |
| Not treated                           | 1                  | -                 | 1                 |

| <b>Number of subjects in period 1</b> | Group 3: 10 mg/kg |
|---------------------------------------|-------------------|
| Started                               | 116               |
| Received treatment                    | 115               |
| Completed                             | 1                 |
| Not completed                         | 115               |

|                                   |    |
|-----------------------------------|----|
| Consent withdrawn by subject      | 2  |
| Treatment ongoing at data cut-off | 5  |
| Adverse event, non-fatal          | 8  |
| Lost to follow-up                 | 2  |
| Lack of efficacy                  | 97 |
| Protocol deviation                | -  |
| Not treated                       | 1  |

## Baseline characteristics

### Reporting groups

|   |                    |
|---|--------------------|
| Reporting group title   | Group 1: 0.3 mg/kg |
| Reporting group description:  |                    |
| Participants received robatumumab 0.3 mg/kg intravenously (IV) as a single dose on Day 1, followed by surgery on Day 10 to 14, and four week later, resumption of robatumumab 0.3 mg/kg on the same calendar day ( $\pm$ 3 days) once every 2 weeks until disease recurrence or up to 1 year of dosing. This group comprised participants with resectable osteosarcoma that relapsed within 6 months of prior definitive treatment (eg surgical metastasectomy) and having at least one prior chemotherapy regimen containing a platinum agent and doxorubicin. |                    |
| Reporting group title   | Group 1: 10 mg/kg  |
| Reporting group description:  |                    |
| Participants who received robatumumab 10 mg/kg IV as a single dose on Day 1, followed by surgery on Day 10 to 14, and four week later, resumption of robatumumab 10 mg/kg on the same calendar day ( $\pm$ 3 days) once every 2 weeks until disease recurrence or up to 1 year of dosing. This group comprised participants with resectable osteosarcoma that relapsed within 6 months of prior definitive treatment (eg surgical metastasectomy) and having at least one prior chemotherapy regimen containing a platinum agent and doxorubicin.               |                    |
| Reporting group title   | Group 2: 10 mg/kg  |
| Reporting group description:  |                    |
| Participants received robatumumab 10 mg/kg IV biweekly until disease recurrence or up to 1 year of dosing. This group comprised participants with relapsed and unresectable osteosarcoma refractory to prior chemotherapy with a platinum- and doxorubicin-containing regimen.  |                    |
| Reporting group title   | Group 3: 10 mg/kg  |
| Reporting group description:  |                    |
| Participants received robatumumab 10 mg/kg IV biweekly until disease recurrence or up to 1 year of dosing. This group comprised participants with Ewing sarcoma refractory to prior treatment with at least 3 of the following agents: ifosfamide, etoposide, cyclophosphamide, doxorubicin, or vincristine.  |                    |

| Reporting group values | Group 1: 0.3 mg/kg | Group 1: 10 mg/kg | Group 2: 10 mg/kg |
|------------------------|--------------------|-------------------|-------------------|
| Number of subjects     | 35                 | 33                | 35                |
| Age categorical        |                    |                   |                   |
| Units: Subjects        |                    |                   |                   |

|                    |            |            |            |
|--------------------|------------|------------|------------|
| Age continuous     |            |            |            |
| Units: years       |            |            |            |
| arithmetic mean    | 23.7       | 20.1       | 27.5       |
| standard deviation | $\pm$ 15.5 | $\pm$ 10.3 | $\pm$ 15.3 |
| Gender categorical |            |            |            |
| Units: Subjects    |            |            |            |
| Female             | 14         | 13         | 11         |
| Male               | 21         | 20         | 24         |

| Reporting group values | Group 3: 10 mg/kg | Total |  |
|------------------------|-------------------|-------|--|
| Number of subjects     | 116               | 219   |  |
| Age categorical        |                   |       |  |
| Units: Subjects        |                   |       |  |

|                 |      |  |  |
|-----------------|------|--|--|
| Age continuous  |      |  |  |
| Units: years    |      |  |  |
| arithmetic mean | 24.6 |  |  |

|                    |            |   |  |
|--------------------|------------|---|--|
| standard deviation | $\pm 11.4$ | - |  |
|--------------------|------------|---|--|

|                    |    |     |  |
|--------------------|----|-----|--|
| Gender categorical |    |     |  |
| Units: Subjects    |    |     |  |
| Female             | 43 | 81  |  |
| Male               | 73 | 138 |  |



## End points

### End points reporting groups

|   |                    |
|---|--------------------|
| Reporting group title   | Group 1: 0.3 mg/kg |
| Reporting group description:<br>Participants received robatumumab 0.3 mg/kg intravenously (IV) as a single dose on Day 1, followed by surgery on Day 10 to 14, and four week later, resumption of robatumumab 0.3 mg/kg on the same calendar day ( $\pm$ 3 days) once every 2 weeks until disease recurrence or up to 1 year of dosing. This group comprised participants with resectable osteosarcoma that relapsed within 6 months of prior definitive treatment (eg surgical metastasectomy) and having at least one prior chemotherapy regimen containing a platinum agent and doxorubicin. |                    |
| Reporting group title   | Group 1: 10 mg/kg  |
| Reporting group description:<br>Participants who received robatumumab 10 mg/kg IV as a single dose on Day 1, followed by surgery on Day 10 to 14, and four week later, resumption of robatumumab 10 mg/kg on the same calendar day ( $\pm$ 3 days) once every 2 weeks until disease recurrence or up to 1 year of dosing. This group comprised participants with resectable osteosarcoma that relapsed within 6 months of prior definitive treatment (eg surgical metastasectomy) and having at least one prior chemotherapy regimen containing a platinum agent and doxorubicin.               |                    |
| Reporting group title   | Group 2: 10 mg/kg  |
| Reporting group description:<br>Participants received robatumumab 10 mg/kg IV biweekly until disease recurrence or up to 1 year of dosing. This group comprised participants with relapsed and unresectable osteosarcoma refractory to prior chemotherapy with a platinum- and doxorubicin-containing regimen.  |                    |
| Reporting group title   | Group 3: 10 mg/kg  |
| Reporting group description:<br>Participants received robatumumab 10 mg/kg IV biweekly until disease recurrence or up to 1 year of dosing. This group comprised participants with Ewing sarcoma refractory to prior treatment with at least 3 of the following agents: ifosfamide, etoposide, cyclophosphamide, doxorubicin, or vincristine.  |                    |

### Primary: Number of Participants Achieving a Complete Response or Partial Response (Group 3)

|  |  |
|--|--|
| End point title  | Number of Participants Achieving a Complete Response or Partial Response (Group 3) <sup>[1][2]</sup> |
| End point description:<br>Response to therapy achieved by study participants in Group 3, confirmed by central review |  |
| End point type   | Primary  |
| End point timeframe:<br>Up to 2 years  |  |

#### Notes:

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

Justification: No statistical analysis was done for this endpoint due to early termination.

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

Justification: This analysis was only planned for Group 3 participants.

|                             |                   |  |  |  |
|-----------------------------|-------------------|--|--|--|
| <b>End point values</b>     | Group 3: 10 mg/kg |  |  |  |
| Subject group type          | Reporting group   |  |  |  |
| Number of subjects analysed | 84 <sup>[3]</sup> |  |  |  |
| Units: Participants         | 6                 |  |  |  |

Notes:

[3] - Participants with evaluable data

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants Achieving a Complete Response, a Partial Response, or Stable disease (Group 2)

|                        |   |
|------------------------|---|
| End point title        | Number of Participants Achieving a Complete Response, a Partial Response, or Stable disease (Group 2) <sup>[4][5]</sup> |
| End point description: | Response to treatment confirmed by central review for participants in Group 2.  |
| End point type         | Primary   |
| End point timeframe:   | Up to 2 years   |

Notes:

[4] - 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: Statistical analysis was not done due to early termination of the study.

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

Justification: The endpoint was only planned for the Group 2 population.

|                             |                   |  |  |  |
|-----------------------------|-------------------|--|--|--|
| End point values            | Group 2: 10 mg/kg |  |  |  |
| Subject group type          | Reporting group   |  |  |  |
| Number of subjects analysed | 25 <sup>[6]</sup> |  |  |  |
| Units: Participants         | 6                 |  |  |  |

Notes:

[6] - Accrual to this arm was stopped due to no responses.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival

|                        |   |
|------------------------|---|
| End point title        | Overall Survival  |
| End point description: | The endpoint is defined as the number of participants known to be alive at the time of data analysis for the study. |
| End point type         | Secondary   |
| End point timeframe:   | Up to 2 years   |

| <b>End point values</b>     | Group 1: 0.3 mg/kg | Group 1: 10 mg/kg | Group 2: 10 mg/kg | Group 3: 10 mg/kg |
|-----------------------------|--------------------|-------------------|-------------------|-------------------|
| Subject group type          | Reporting group    | Reporting group   | Reporting group   | Reporting group   |
| Number of subjects analysed | 35                 | 33                | 35                | 116               |
| Units: Participants         | 17                 | 16                | 7                 | 28                |

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events are reported from enrollment up to 5 weeks after the end of treatment.

Adverse event reporting additional description:

3 participants in Group 1 experienced adverse events prior to beginning treatment; 3 participants did not receive study therapy (1 in Group 1 0.3 mg, 1 in Group 1 10 mg, and 1 in Group 3).

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 14.0 |
|--------------------|------|

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Group 1: 0.3mg/kg |
|-----------------------|-------------------|

Reporting group description: -

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Group 3: 10mg/kg |
|-----------------------|------------------|

Reporting group description: -

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Group 2: 10mg/kg |
|-----------------------|------------------|

Reporting group description: -

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Group 1: 10mg/kg |
|-----------------------|------------------|

Reporting group description: -

| Serious adverse events  | Group 1: 0.3mg/kg | Group 3: 10mg/kg  | Group 2: 10mg/kg |
|---|-------------------|-------------------|------------------|
| Total subjects affected by serious adverse events                   |                   |                   |                  |
| subjects affected / exposed   | 17 / 34 (50.00%)  | 57 / 115 (49.57%) | 12 / 34 (35.29%) |
| number of deaths (all causes)                                       | 6                 | 14                | 1                |
| number of deaths resulting from adverse events                      | 1                 | 1                 | 0                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |                  |
| Cancer Pain   |                   |                   |                  |
| subjects affected / exposed   | 0 / 34 (0.00%)    | 1 / 115 (0.87%)   | 0 / 34 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1             | 0 / 0            |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             | 0 / 0            |
| Malignant Pleural Effusion  |                   |                   |                  |
| subjects affected / exposed   | 0 / 34 (0.00%)    | 0 / 115 (0.00%)   | 1 / 34 (2.94%)   |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 0             | 0 / 1            |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             | 0 / 0            |
| Metastases To Lung  |                   |                   |                  |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 34 (2.94%) | 0 / 115 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0           | 0 / 0          |
| Osteosarcoma Recurrent                          |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 0 / 115 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Tumour Pain                                     |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 3 / 115 (2.61%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Vascular disorders                              |                |                 |                |
| Haemorrhage                                     |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Hypotension                                     |                |                 |                |
| subjects affected / exposed                     | 1 / 34 (2.94%) | 0 / 115 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Shock Haemorrhagic                              |                |                 |                |
| subjects affected / exposed                     | 1 / 34 (2.94%) | 0 / 115 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 0           | 0 / 0          |
| Surgical and medical procedures                 |                |                 |                |
| Leg Amputation                                  |                |                 |                |
| subjects affected / exposed                     | 1 / 34 (2.94%) | 0 / 115 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Medical Device Removal                          |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Thoracotomy                                     |                |                 |                |

|  |                |                 |                |
|--|----------------|-----------------|----------------|
| subjects affected / exposed                          | 1 / 34 (2.94%) | 0 / 115 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0          |
| Wound Treatment                                      |                |                 |                |
| subjects affected / exposed                          | 1 / 34 (2.94%) | 0 / 115 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0          |
| General disorders and administration site conditions |                |                 |                |
| Asthenia   |                |                 |                |
| subjects affected / exposed                          | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0          |
| Chest Pain   |                |                 |                |
| subjects affected / exposed                          | 0 / 34 (0.00%) | 4 / 115 (3.48%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 4           | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0          |
| Condition Aggravated                                 |                |                 |                |
| subjects affected / exposed                          | 1 / 34 (2.94%) | 0 / 115 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0          |
| Device Dislocation                                   |                |                 |                |
| subjects affected / exposed                          | 1 / 34 (2.94%) | 0 / 115 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0          |
| Drug Withdrawal Syndrome                             |                |                 |                |
| subjects affected / exposed                          | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0          |
| Fatigue  |                |                 |                |
| subjects affected / exposed                          | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0          |
| General Physical Health* Deterioration               |                |                 |                |

|   |                |                  |                |
|---|----------------|------------------|----------------|
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%)  | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0          |
| Hyperthermia                                    |                |                  |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%)  | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0          |
| Influenza Like Illness                          |                |                  |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%)  | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0          |
| Malaise   |                |                  |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%)  | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0          |
| Mucosal Inflammation                            |                |                  |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%)  | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0          |
| Multi-Organ Failure                             |                |                  |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%)  | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1            | 0 / 0          |
| Oedema Peripheral                               |                |                  |                |
| subjects affected / exposed                     | 1 / 34 (2.94%) | 0 / 115 (0.00%)  | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0            | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0          |
| Pain  |                |                  |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 11 / 115 (9.57%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 13           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0          |
| Performance Status Decreased                    |                |                  |                |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Pyrexia   |                |                 |                |
| subjects affected / exposed                     | 1 / 34 (2.94%) | 7 / 115 (6.09%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 11          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                |                 |                |
| Acute respiratory distress syndrome             |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Acute Respiratory Failure                       |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 2 / 115 (1.74%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 2           | 0 / 0          |
| Bronchial Disorder                              |                |                 |                |
| subjects affected / exposed                     | 1 / 34 (2.94%) | 0 / 115 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Dyspnoea  |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 3 / 115 (2.61%) | 2 / 34 (5.88%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Dyspnoea At Rest                                |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 0 / 115 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Dyspnoea Exertional                             |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Epistaxis                                       |                |                 |                |



|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 34 (0.00%)  | 2 / 115 (1.74%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Haemothorax                                     |                 |                 |                |
| subjects affected / exposed                     | 1 / 34 (2.94%)  | 0 / 115 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hypoxia   |                 |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%)  | 0 / 115 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1          |
| Pleural Effusion                                |                 |                 |                |
| subjects affected / exposed                     | 1 / 34 (2.94%)  | 0 / 115 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pneumothorax                                    |                 |                 |                |
| subjects affected / exposed                     | 4 / 34 (11.76%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pulmonary Embolism                              |                 |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%)  | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pulmonary Toxicity                              |                 |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%)  | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Respiratory Distress                            |                 |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%)  | 6 / 115 (5.22%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 7           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 2           | 0 / 0          |
| Respiratory Failure                             |                 |                 |                |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed                     | 3 / 34 (8.82%) | 5 / 115 (4.35%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 5           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 3          | 0 / 5           | 0 / 0          |
| <b>Psychiatric disorders</b>                    |                |                 |                |
| <b>Agitation</b>                                |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 0 / 115 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| <b>Anxiety</b>                                  |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 0 / 115 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| <b>Confusional State</b>                        |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 0 / 115 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| <b>Insomnia</b>                                 |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 0 / 115 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| <b>Mental Status Changes</b>                    |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| <b>Investigations</b>                           |                |                 |                |
| <b>Biopsy Bone Abnormal</b>                     |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 0 / 115 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| <b>Blood Potassium Decreased</b>                |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 0 / 115 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| <b>Injury, poisoning and procedural</b>         |                |                 |                |

|   |                |                 |                |  |
|---|----------------|-----------------|----------------|--|
| complications                                   |                |                 |                |  |
| Brain Herniation                                |                |                 |                |  |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0          |  |
| Humerus Fracture                                |                |                 |                |  |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 0 / 115 (0.00%) | 1 / 34 (2.94%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |  |
| Postoperative Respiratory* Distress             |                |                 |                |  |
| subjects affected / exposed                     | 1 / 34 (2.94%) | 0 / 115 (0.00%) | 0 / 34 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |  |
| Procedural Hypotension                          |                |                 |                |  |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 0 / 115 (0.00%) | 1 / 34 (2.94%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |  |
| Rib Fracture                                    |                |                 |                |  |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |  |
| Toxicity To Various Agents                      |                |                 |                |  |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |  |
| Wound Necrosis                                  |                |                 |                |  |
| subjects affected / exposed                     | 1 / 34 (2.94%) | 0 / 115 (0.00%) | 0 / 34 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |  |
| Congenital, familial and genetic disorders      |                |                 |                |  |
| Aplasia   |                |                 |                |  |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| <b>Cardiac disorders</b>                        |                |                 |                |
| Atrial Fibrillation                             |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 0 / 115 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Cardiac Failure                                 |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0          |
| Cardio-Respiratory Arrest                       |                |                 |                |
| subjects affected / exposed                     | 1 / 34 (2.94%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0           | 0 / 0          |
| Tachycardia                                     |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| <b>Nervous system disorders</b>                 |                |                 |                |
| Altered State Of Consciousness                  |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Coma  |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0          |
| Convulsion                                      |                |                 |                |
| subjects affected / exposed                     | 1 / 34 (2.94%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Encephalopathy                                  |                |                 |                |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 34 (0.00%) | 2 / 115 (1.74%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 2           | 0 / 0          |
| Headache  |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Hepatic Encephalopathy                          |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Meningeal Disorder                              |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Myoclonus                                       |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Nerve Compression                               |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Peripheral Sensory Neuropathy                   |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Spinal Cord Compression                         |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 2 / 115 (1.74%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Syncope   |                |                 |                |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Toxic Encephalopathy                            |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Blood and lymphatic system disorders            |                |                 |                |
| Anaemia   |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 3 / 115 (2.61%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 3           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Febrile Bone Marrow Aplasia                     |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Febrile Neutropenia                             |                |                 |                |
| subjects affected / exposed                     | 2 / 34 (5.88%) | 0 / 115 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Thrombocytopenia                                |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 4 / 115 (3.48%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 3 / 6           | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Eye disorders                                   |                |                 |                |
| Blindness Unilateral                            |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Vision Blurred                                  |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Gastrointestinal disorders                      |                |                 |                |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| Abdominal Pain                                  |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 3 / 115 (2.61%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Constipation                                    |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 2 / 115 (1.74%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Diarrhoea                                       |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Gastrointestinal Pain                           |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Ileus   |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Nausea  |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Retroperitoneal Haemorrhage                     |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Upper Gastrointestinal*<br>Haemorrhage          |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Vomiting  |                |                 |                |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 34 (0.00%) | 2 / 115 (1.74%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Hepatobiliary disorders                         |                |                 |                |
| Hepatic Haemorrhage                             |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Jaundice  |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Skin and subcutaneous tissue disorders          |                |                 |                |
| Petechiae                                       |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Renal and urinary disorders                     |                |                 |                |
| Nephrolithiasis                                 |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                |                 |                |
| Arthralgia                                      |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 2 / 115 (1.74%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Back Pain                                       |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 3 / 115 (2.61%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 4           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Bursitis  |                |                 |                |



|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 34 (0.00%) | 0 / 115 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Flank Pain                                      |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Hypercreatinaemia                               |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 0 / 115 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Musculoskeletal Pain                            |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Infections and infestations                     |                |                 |                |
| Appendicitis                                    |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Bronchopneumonia                                |                |                 |                |
| subjects affected / exposed                     | 1 / 34 (2.94%) | 0 / 115 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Central Nervous System* Infection               |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Gastroenteritis                                 |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Gastroenteritis Viral                           |                |                 |                |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Herpes Zoster                                   |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Infection                                       |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Otitis Media                                    |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Pneumonia                                       |                |                 |                |
| subjects affected / exposed                     | 1 / 34 (2.94%) | 2 / 115 (1.74%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Pneumonia Viral                                 |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Post Procedural Infection                       |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 0 / 115 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Postoperative Wound Infection                   |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 0 / 115 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Sepsis  |                |                 |                |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Urinary Tract Infection                         |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 115 (0.87%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Metabolism and nutrition disorders              |                |                 |                |
| Decreased Appetite                              |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 2 / 115 (1.74%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Hyperglycaemia                                  |                |                 |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 0 / 115 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |

|   |                  |  |  |
|---|------------------|--|--|
| <b>Serious adverse events</b>                                       | Group 1: 10mg/kg |  |  |
| Total subjects affected by serious adverse events                   |                  |  |  |
| subjects affected / exposed   | 8 / 33 (24.24%)  |  |  |
| number of deaths (all causes)                                       | 1                |  |  |
| number of deaths resulting from adverse events                      | 0                |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |  |  |
| Cancer Pain   |                  |  |  |
| subjects affected / exposed   | 0 / 33 (0.00%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 0            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Malignant Pleural Effusion  |                  |  |  |
| subjects affected / exposed   | 0 / 33 (0.00%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 0            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Metastases To Lung  |                  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Osteosarcoma Recurrent                          |                |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Tumour Pain                                     |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Vascular disorders                              |                |  |  |
| Haemorrhage                                     |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hypotension                                     |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Shock Haemorrhagic                              |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Surgical and medical procedures                 |                |  |  |
| Leg Amputation                                  |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Medical Device Removal                          |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Thoracotomy                                     |                |  |  |

|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                          | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Wound Treatment                                      |                |  |  |
| subjects affected / exposed                          | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Asthenia   |                |  |  |
| subjects affected / exposed                          | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Chest Pain   |                |  |  |
| subjects affected / exposed                          | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Condition Aggravated                                 |                |  |  |
| subjects affected / exposed                          | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Device Dislocation                                   |                |  |  |
| subjects affected / exposed                          | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Drug Withdrawal Syndrome                             |                |  |  |
| subjects affected / exposed                          | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Fatigue  |                |  |  |
| subjects affected / exposed                          | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General Physical Health* Deterioration               |                |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Hyperthermia                                    |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Influenza Like Illness                          |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Malaise   |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Mucosal Inflammation                            |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Multi-Organ Failure                             |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Oedema Peripheral                               |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pain  |                |  |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Performance Status Decreased                    |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pyrexia   |                |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Acute respiratory distress syndrome             |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Acute Respiratory Failure                       |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Bronchial Disorder                              |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dyspnoea  |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dyspnoea At Rest                                |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dyspnoea Exertional                             |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Epistaxis                                       |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Haemothorax                                     |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hypoxia   |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pleural Effusion                                |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumothorax                                    |                |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pulmonary Embolism                              |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pulmonary Toxicity                              |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory Distress                            |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory Failure                             |                |  |  |



|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 33 (3.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Psychiatric disorders                           |                |  |  |
| Agitation                                       |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Anxiety   |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Confusional State                               |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Insomnia  |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Mental Status Changes                           |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Investigations                                  |                |  |  |
| Biopsy Bone Abnormal                            |                |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Blood Potassium Decreased                       |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Injury, poisoning and procedural                |                |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| complications                                   |                |  |  |  |
| Brain Herniation                                |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Humerus Fracture                                |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Postoperative Respiratory* Distress             |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Procedural Hypotension                          |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Rib Fracture                                    |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Toxicity To Various Agents                      |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Wound Necrosis                                  |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Congenital, familial and genetic disorders      |                |  |  |  |
| Aplasia   |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac disorders                               |                |  |  |
| Atrial Fibrillation                             |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac Failure                                 |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardio-Respiratory Arrest                       |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Tachycardia                                     |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nervous system disorders                        |                |  |  |
| Altered State Of Consciousness                  |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Coma  |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Convulsion                                      |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Encephalopathy                                  |                |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Headache  |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Hepatic Encephalopathy                          |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Meningeal Disorder                              |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Myoclonus                                       |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Nerve Compression                               |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Peripheral Sensory Neuropathy                   |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Spinal Cord Compression                         |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Syncope   |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Toxic Encephalopathy                            |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Blood and lymphatic system disorders            |                |  |  |
| Anaemia   |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Febrile Bone Marrow Aplasia                     |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Febrile Neutropenia                             |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Thrombocytopenia                                |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Eye disorders                                   |                |  |  |
| Blindness Unilateral                            |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Vision Blurred                                  |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal disorders                      |                |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| Abdominal Pain                                  |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Constipation                                    |                |  |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Diarrhoea                                       |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Gastrointestinal Pain                           |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Ileus   |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Nausea  |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Retroperitoneal Haemorrhage                     |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Upper Gastrointestinal*<br>Haemorrhage          |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Vomiting  |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hepatobiliary disorders                         |                |  |  |
| Hepatic Haemorrhage                             |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Jaundice  |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Skin and subcutaneous tissue disorders          |                |  |  |
| Petechiae                                       |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal and urinary disorders                     |                |  |  |
| Nephrolithiasis                                 |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| Arthralgia                                      |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Back Pain                                       |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Bursitis  |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Flank Pain                                      |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hypercreatinaemia                               |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal Pain                            |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Appendicitis                                    |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Bronchopneumonia                                |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Central Nervous System* Infection               |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastroenteritis                                 |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastroenteritis Viral                           |                |  |  |



|   |                |  |  |  |
|---|----------------|--|--|--|
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Herpes Zoster                                   |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Infection                                       |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Otitis Media                                    |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pneumonia                                       |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pneumonia Viral                                 |                |  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Post Procedural Infection                       |                |  |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Postoperative Wound Infection                   |                |  |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Sepsis  |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Urinary Tract Infection                         |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Metabolism and nutrition disorders              |                |  |  |
| Decreased Appetite                              |                |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hyperglycaemia                                  |                |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                                   | Group 1: 0.3mg/kg | Group 3: 10mg/kg   | Group 2: 10mg/kg |
|---|-------------------|--------------------|------------------|
| Total subjects affected by non-serious adverse events               |                   |                    |                  |
| subjects affected / exposed   | 28 / 34 (82.35%)  | 104 / 115 (90.43%) | 29 / 34 (85.29%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                    |                  |
| Tumour Pain   |                   |                    |                  |
| subjects affected / exposed   | 0 / 34 (0.00%)    | 8 / 115 (6.96%)    | 2 / 34 (5.88%)   |
| occurrences (all)   | 0                 | 11                 | 2                |
| Vascular disorders  |                   |                    |                  |
| Hypotension   |                   |                    |                  |
| subjects affected / exposed   | 2 / 34 (5.88%)    | 6 / 115 (5.22%)    | 2 / 34 (5.88%)   |
| occurrences (all)   | 2                 | 6                  | 2                |
| General disorders and administration site conditions                |                   |                    |                  |
| Asthenia  |                   |                    |                  |
| subjects affected / exposed   | 0 / 34 (0.00%)    | 13 / 115 (11.30%)  | 1 / 34 (2.94%)   |
| occurrences (all)   | 0                 | 18                 | 1                |
| Chest Pain  |                   |                    |                  |

|   |                  |                   |                 |
|---|------------------|-------------------|-----------------|
| subjects affected / exposed                     | 7 / 34 (20.59%)  | 10 / 115 (8.70%)  | 3 / 34 (8.82%)  |
| occurrences (all)                               | 8                | 12                | 3               |
| Fatigue   |                  |                   |                 |
| subjects affected / exposed                     | 7 / 34 (20.59%)  | 23 / 115 (20.00%) | 7 / 34 (20.59%) |
| occurrences (all)                               | 10               | 28                | 7               |
| Mucosal Inflammation                            |                  |                   |                 |
| subjects affected / exposed                     | 0 / 34 (0.00%)   | 0 / 115 (0.00%)   | 0 / 34 (0.00%)  |
| occurrences (all)                               | 0                | 0                 | 0               |
| Oedema Peripheral                               |                  |                   |                 |
| subjects affected / exposed                     | 2 / 34 (5.88%)   | 4 / 115 (3.48%)   | 3 / 34 (8.82%)  |
| occurrences (all)                               | 2                | 4                 | 3               |
| Pain  |                  |                   |                 |
| subjects affected / exposed                     | 4 / 34 (11.76%)  | 9 / 115 (7.83%)   | 2 / 34 (5.88%)  |
| occurrences (all)                               | 4                | 11                | 2               |
| Pyrexia   |                  |                   |                 |
| subjects affected / exposed                     | 9 / 34 (26.47%)  | 21 / 115 (18.26%) | 6 / 34 (17.65%) |
| occurrences (all)                               | 11               | 37                | 7               |
| Respiratory, thoracic and mediastinal disorders |                  |                   |                 |
| Cough   |                  |                   |                 |
| subjects affected / exposed                     | 10 / 34 (29.41%) | 16 / 115 (13.91%) | 6 / 34 (17.65%) |
| occurrences (all)                               | 10               | 19                | 6               |
| Dyspnoea  |                  |                   |                 |
| subjects affected / exposed                     | 6 / 34 (17.65%)  | 7 / 115 (6.09%)   | 4 / 34 (11.76%) |
| occurrences (all)                               | 7                | 7                 | 4               |
| Dyspnoea Exertional                             |                  |                   |                 |
| subjects affected / exposed                     | 4 / 34 (11.76%)  | 11 / 115 (9.57%)  | 2 / 34 (5.88%)  |
| occurrences (all)                               | 5                | 11                | 2               |
| Epistaxis                                       |                  |                   |                 |
| subjects affected / exposed                     | 3 / 34 (8.82%)   | 9 / 115 (7.83%)   | 0 / 34 (0.00%)  |
| occurrences (all)                               | 6                | 11                | 0               |
| Haemoptysis                                     |                  |                   |                 |
| subjects affected / exposed                     | 3 / 34 (8.82%)   | 2 / 115 (1.74%)   | 2 / 34 (5.88%)  |
| occurrences (all)                               | 3                | 3                 | 3               |
| Oropharyngeal Pain                              |                  |                   |                 |

|                             |                 |                   |                |
|-----------------------------|-----------------|-------------------|----------------|
| subjects affected / exposed | 3 / 34 (8.82%)  | 11 / 115 (9.57%)  | 2 / 34 (5.88%) |
| occurrences (all)           | 4               | 15                | 2              |
| Pleural Effusion            |                 |                   |                |
| subjects affected / exposed | 3 / 34 (8.82%)  | 6 / 115 (5.22%)   | 1 / 34 (2.94%) |
| occurrences (all)           | 4               | 6                 | 2              |
| Pneumothorax                |                 |                   |                |
| subjects affected / exposed | 4 / 34 (11.76%) | 2 / 115 (1.74%)   | 1 / 34 (2.94%) |
| occurrences (all)           | 5               | 2                 | 1              |
| Rhinorrhoea                 |                 |                   |                |
| subjects affected / exposed | 1 / 34 (2.94%)  | 1 / 115 (0.87%)   | 1 / 34 (2.94%) |
| occurrences (all)           | 1               | 1                 | 1              |
| Wheezing                    |                 |                   |                |
| subjects affected / exposed | 3 / 34 (8.82%)  | 3 / 115 (2.61%)   | 0 / 34 (0.00%) |
| occurrences (all)           | 4               | 4                 | 0              |
| Psychiatric disorders       |                 |                   |                |
| Anxiety                     |                 |                   |                |
| subjects affected / exposed | 2 / 34 (5.88%)  | 18 / 115 (15.65%) | 3 / 34 (8.82%) |
| occurrences (all)           | 2               | 24                | 3              |
| Depression                  |                 |                   |                |
| subjects affected / exposed | 1 / 34 (2.94%)  | 4 / 115 (3.48%)   | 2 / 34 (5.88%) |
| occurrences (all)           | 1               | 4                 | 2              |
| Insomnia                    |                 |                   |                |
| subjects affected / exposed | 4 / 34 (11.76%) | 20 / 115 (17.39%) | 2 / 34 (5.88%) |
| occurrences (all)           | 4               | 20                | 2              |
| Investigations              |                 |                   |                |
| Aspartate Aminotransferase* |                 |                   |                |
| Increased                   |                 |                   |                |
| subjects affected / exposed | 0 / 34 (0.00%)  | 8 / 115 (6.96%)   | 0 / 34 (0.00%) |
| occurrences (all)           | 0               | 11                | 0              |
| Blood Alkaline Phosphatase* |                 |                   |                |
| Increased                   |                 |                   |                |
| subjects affected / exposed | 1 / 34 (2.94%)  | 3 / 115 (2.61%)   | 1 / 34 (2.94%) |
| occurrences (all)           | 1               | 3                 | 1              |
| Gamma-Glutamyltransferase*  |                 |                   |                |
| Increased                   |                 |                   |                |
| subjects affected / exposed | 0 / 34 (0.00%)  | 9 / 115 (7.83%)   | 0 / 34 (0.00%) |
| occurrences (all)           | 0               | 11                | 0              |
| Haemoglobin Decreased       |                 |                   |                |

|  |                        |                         |                       |
|--|------------------------|-------------------------|-----------------------|
| subjects affected / exposed<br>occurrences (all)                                   | 5 / 34 (14.71%)<br>6   | 3 / 115 (2.61%)<br>4    | 1 / 34 (2.94%)<br>1   |
| Platelet Count Decreased<br>subjects affected / exposed<br>occurrences (all)       | 3 / 34 (8.82%)<br>4    | 2 / 115 (1.74%)<br>6    | 0 / 34 (0.00%)<br>0   |
| Weight Decreased<br>subjects affected / exposed<br>occurrences (all)               | 1 / 34 (2.94%)<br>1    | 11 / 115 (9.57%)<br>13  | 2 / 34 (5.88%)<br>2   |
| Injury, poisoning and procedural complications                                     |                        |                         |                       |
| Incision Site Pain<br>subjects affected / exposed<br>occurrences (all)             | 1 / 34 (2.94%)<br>1    | 2 / 115 (1.74%)<br>3    | 1 / 34 (2.94%)<br>1   |
| Post Procedural Haemorrhage<br>subjects affected / exposed<br>occurrences (all)    | 2 / 34 (5.88%)<br>2    | 0 / 115 (0.00%)<br>0    | 0 / 34 (0.00%)<br>0   |
| Post-Thoracotomy Pain Syndrome<br>subjects affected / exposed<br>occurrences (all) | 3 / 34 (8.82%)<br>3    | 0 / 115 (0.00%)<br>0    | 1 / 34 (2.94%)<br>1   |
| Procedural Pain<br>subjects affected / exposed<br>occurrences (all)                | 13 / 34 (38.24%)<br>16 | 2 / 115 (1.74%)<br>2    | 1 / 34 (2.94%)<br>1   |
| Cardiac disorders  |                        |                         |                       |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)                    | 2 / 34 (5.88%)<br>2    | 4 / 115 (3.48%)<br>4    | 1 / 34 (2.94%)<br>1   |
| Sinus Tachycardia<br>subjects affected / exposed<br>occurrences (all)              | 2 / 34 (5.88%)<br>2    | 0 / 115 (0.00%)<br>0    | 0 / 34 (0.00%)<br>0   |
| Nervous system disorders   |                        |                         |                       |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 34 (2.94%)<br>1    | 7 / 115 (6.09%)<br>10   | 0 / 34 (0.00%)<br>0   |
| Headache<br>subjects affected / exposed<br>occurrences (all)                       | 9 / 34 (26.47%)<br>16  | 24 / 115 (20.87%)<br>57 | 7 / 34 (20.59%)<br>10 |
| Somnolence   |                        |                         |                       |

|  |                     |                      |                     |
|--|---------------------|----------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 1 / 34 (2.94%)<br>1 | 7 / 115 (6.09%)<br>9 | 0 / 34 (0.00%)<br>0 |
| Blood and lymphatic system disorders             |                     |                      |                     |
| Anaemia  |                     |                      |                     |
| subjects affected / exposed                      | 6 / 34 (17.65%)     | 22 / 115 (19.13%)    | 3 / 34 (8.82%)      |
| occurrences (all)                                | 8                   | 44                   | 4                   |
| Thrombocytopenia                                 |                     |                      |                     |
| subjects affected / exposed                      | 1 / 34 (2.94%)      | 17 / 115 (14.78%)    | 1 / 34 (2.94%)      |
| occurrences (all)                                | 2                   | 35                   | 1                   |
| Leukopenia                                       |                     |                      |                     |
| subjects affected / exposed                      | 1 / 34 (2.94%)      | 3 / 115 (2.61%)      | 0 / 34 (0.00%)      |
| occurrences (all)                                | 1                   | 4                    | 0                   |
| Neutropenia                                      |                     |                      |                     |
| subjects affected / exposed                      | 0 / 34 (0.00%)      | 6 / 115 (5.22%)      | 0 / 34 (0.00%)      |
| occurrences (all)                                | 0                   | 6                    | 0                   |
| Ear and labyrinth disorders                      |                     |                      |                     |
| Tinnitus   |                     |                      |                     |
| subjects affected / exposed                      | 2 / 34 (5.88%)      | 1 / 115 (0.87%)      | 0 / 34 (0.00%)      |
| occurrences (all)                                | 2                   | 1                    | 0                   |
| Gastrointestinal disorders                       |                     |                      |                     |
| Abdominal Pain                                   |                     |                      |                     |
| subjects affected / exposed                      | 1 / 34 (2.94%)      | 9 / 115 (7.83%)      | 0 / 34 (0.00%)      |
| occurrences (all)                                | 1                   | 13                   | 0                   |
| Abdominal Pain Upper                             |                     |                      |                     |
| subjects affected / exposed                      | 2 / 34 (5.88%)      | 9 / 115 (7.83%)      | 1 / 34 (2.94%)      |
| occurrences (all)                                | 2                   | 10                   | 1                   |
| Constipation                                     |                     |                      |                     |
| subjects affected / exposed                      | 9 / 34 (26.47%)     | 34 / 115 (29.57%)    | 3 / 34 (8.82%)      |
| occurrences (all)                                | 9                   | 43                   | 3                   |
| Diarrhoea  |                     |                      |                     |
| subjects affected / exposed                      | 3 / 34 (8.82%)      | 29 / 115 (25.22%)    | 2 / 34 (5.88%)      |
| occurrences (all)                                | 6                   | 42                   | 2                   |
| Dyspepsia  |                     |                      |                     |
| subjects affected / exposed                      | 1 / 34 (2.94%)      | 4 / 115 (3.48%)      | 2 / 34 (5.88%)      |
| occurrences (all)                                | 1                   | 5                    | 2                   |
| Gastrooesophageal Reflux*<br>Disease             |                     |                      |                     |

|  |                        |                         |                      |
|--|------------------------|-------------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                           | 1 / 34 (2.94%)<br>1    | 6 / 115 (5.22%)<br>6    | 0 / 34 (0.00%)<br>0  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                 | 13 / 34 (38.24%)<br>20 | 35 / 115 (30.43%)<br>48 | 5 / 34 (14.71%)<br>6 |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)             | 2 / 34 (5.88%)<br>2    | 6 / 115 (5.22%)<br>6    | 0 / 34 (0.00%)<br>0  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)               | 9 / 34 (26.47%)<br>12  | 25 / 115 (21.74%)<br>40 | 3 / 34 (8.82%)<br>4  |
| Skin and subcutaneous tissue disorders                                     |                        |                         |                      |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)               | 1 / 34 (2.94%)<br>1    | 1 / 115 (0.87%)<br>1    | 0 / 34 (0.00%)<br>0  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)               | 6 / 34 (17.65%)<br>8   | 5 / 115 (4.35%)<br>6    | 2 / 34 (5.88%)<br>2  |
| Rash<br>subjects affected / exposed<br>occurrences (all)                   | 3 / 34 (8.82%)<br>6    | 11 / 115 (9.57%)<br>12  | 1 / 34 (2.94%)<br>1  |
| Subcutaneous Emphysema<br>subjects affected / exposed<br>occurrences (all) | 2 / 34 (5.88%)<br>2    | 1 / 115 (0.87%)<br>1    | 0 / 34 (0.00%)<br>0  |
| Urticaria<br>subjects affected / exposed<br>occurrences (all)              | 3 / 34 (8.82%)<br>4    | 1 / 115 (0.87%)<br>1    | 0 / 34 (0.00%)<br>0  |
| Renal and urinary disorders  |                        |                         |                      |
| Dysuria<br>subjects affected / exposed<br>occurrences (all)                | 0 / 34 (0.00%)<br>0    | 2 / 115 (1.74%)<br>3    | 3 / 34 (8.82%)<br>3  |
| Musculoskeletal and connective tissue disorders                            |                        |                         |                      |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)             | 4 / 34 (11.76%)<br>4   | 10 / 115 (8.70%)<br>12  | 3 / 34 (8.82%)<br>3  |
| Bone Pain  |                        |                         |                      |

|                             |                 |                   |                 |
|-----------------------------|-----------------|-------------------|-----------------|
| subjects affected / exposed | 0 / 34 (0.00%)  | 6 / 115 (5.22%)   | 4 / 34 (11.76%) |
| occurrences (all)           | 0               | 6                 | 4               |
| Back Pain                   |                 |                   |                 |
| subjects affected / exposed | 5 / 34 (14.71%) | 15 / 115 (13.04%) | 6 / 34 (17.65%) |
| occurrences (all)           | 5               | 19                | 7               |
| Muscle Spasms               |                 |                   |                 |
| subjects affected / exposed | 2 / 34 (5.88%)  | 11 / 115 (9.57%)  | 2 / 34 (5.88%)  |
| occurrences (all)           | 3               | 13                | 2               |
| Flank Pain                  |                 |                   |                 |
| subjects affected / exposed | 1 / 34 (2.94%)  | 2 / 115 (1.74%)   | 2 / 34 (5.88%)  |
| occurrences (all)           | 1               | 5                 | 3               |
| Muscular Weakness           |                 |                   |                 |
| subjects affected / exposed | 0 / 34 (0.00%)  | 3 / 115 (2.61%)   | 2 / 34 (5.88%)  |
| occurrences (all)           | 0               | 3                 | 2               |
| Musculoskeletal Chest Pain  |                 |                   |                 |
| subjects affected / exposed | 0 / 34 (0.00%)  | 7 / 115 (6.09%)   | 4 / 34 (11.76%) |
| occurrences (all)           | 0               | 8                 | 4               |
| Musculoskeletal Pain        |                 |                   |                 |
| subjects affected / exposed | 3 / 34 (8.82%)  | 13 / 115 (11.30%) | 1 / 34 (2.94%)  |
| occurrences (all)           | 3               | 16                | 1               |
| Myalgia                     |                 |                   |                 |
| subjects affected / exposed | 1 / 34 (2.94%)  | 6 / 115 (5.22%)   | 2 / 34 (5.88%)  |
| occurrences (all)           | 1               | 7                 | 2               |
| Neck Pain                   |                 |                   |                 |
| subjects affected / exposed | 0 / 34 (0.00%)  | 6 / 115 (5.22%)   | 2 / 34 (5.88%)  |
| occurrences (all)           | 0               | 6                 | 2               |
| Pain In Extremity           |                 |                   |                 |
| subjects affected / exposed | 7 / 34 (20.59%) | 12 / 115 (10.43%) | 6 / 34 (17.65%) |
| occurrences (all)           | 9               | 25                | 8               |
| Pain In Jaw                 |                 |                   |                 |
| subjects affected / exposed | 2 / 34 (5.88%)  | 2 / 115 (1.74%)   | 0 / 34 (0.00%)  |
| occurrences (all)           | 2               | 2                 | 0               |
| Infections and infestations |                 |                   |                 |
| Bronchitis                  |                 |                   |                 |
| subjects affected / exposed | 2 / 34 (5.88%)  | 0 / 115 (0.00%)   | 1 / 34 (2.94%)  |
| occurrences (all)           | 2               | 0                 | 1               |



|                                    |                 |                   |                 |
|------------------------------------|-----------------|-------------------|-----------------|
| Nasopharyngitis                    |                 |                   |                 |
| subjects affected / exposed        | 1 / 34 (2.94%)  | 1 / 115 (0.87%)   | 2 / 34 (5.88%)  |
| occurrences (all)                  | 1               | 2                 | 2               |
| Rhinitis                           |                 |                   |                 |
| subjects affected / exposed        | 2 / 34 (5.88%)  | 2 / 115 (1.74%)   | 0 / 34 (0.00%)  |
| occurrences (all)                  | 2               | 2                 | 0               |
| Sinusitis                          |                 |                   |                 |
| subjects affected / exposed        | 2 / 34 (5.88%)  | 5 / 115 (4.35%)   | 0 / 34 (0.00%)  |
| occurrences (all)                  | 2               | 6                 | 0               |
| Upper Respiratory Tract* Infection |                 |                   |                 |
| subjects affected / exposed        | 7 / 34 (20.59%) | 7 / 115 (6.09%)   | 1 / 34 (2.94%)  |
| occurrences (all)                  | 7               | 13                | 1               |
| Urinary Tract Infection            |                 |                   |                 |
| subjects affected / exposed        | 1 / 34 (2.94%)  | 8 / 115 (6.96%)   | 4 / 34 (11.76%) |
| occurrences (all)                  | 1               | 12                | 4               |
| Metabolism and nutrition disorders |                 |                   |                 |
| Decreased Appetite                 |                 |                   |                 |
| subjects affected / exposed        | 5 / 34 (14.71%) | 27 / 115 (23.48%) | 4 / 34 (11.76%) |
| occurrences (all)                  | 6               | 37                | 4               |
| Dehydration                        |                 |                   |                 |
| subjects affected / exposed        | 0 / 34 (0.00%)  | 6 / 115 (5.22%)   | 1 / 34 (2.94%)  |
| occurrences (all)                  | 0               | 6                 | 1               |
| Hyperglycaemia                     |                 |                   |                 |
| subjects affected / exposed        | 6 / 34 (17.65%) | 12 / 115 (10.43%) | 1 / 34 (2.94%)  |
| occurrences (all)                  | 11              | 18                | 1               |
| Hypoalbuminaemia                   |                 |                   |                 |
| subjects affected / exposed        | 2 / 34 (5.88%)  | 5 / 115 (4.35%)   | 0 / 34 (0.00%)  |
| occurrences (all)                  | 2               | 5                 | 0               |
| Hypocalcaemia                      |                 |                   |                 |
| subjects affected / exposed        | 3 / 34 (8.82%)  | 4 / 115 (3.48%)   | 2 / 34 (5.88%)  |
| occurrences (all)                  | 6               | 8                 | 2               |
| Hypokalaemia                       |                 |                   |                 |
| subjects affected / exposed        | 3 / 34 (8.82%)  | 6 / 115 (5.22%)   | 0 / 34 (0.00%)  |
| occurrences (all)                  | 4               | 8                 | 0               |
| Hyponatraemia                      |                 |                   |                 |

|                             |                 |                 |                |
|-----------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 4 / 34 (11.76%) | 2 / 115 (1.74%) | 1 / 34 (2.94%) |
| occurrences (all)           | 5               | 2               | 1              |
| Hypophosphataemia           |                 |                 |                |
| subjects affected / exposed | 1 / 34 (2.94%)  | 2 / 115 (1.74%) | 1 / 34 (2.94%) |
| occurrences (all)           | 1               | 2               | 1              |

|   |                  |  |  |
|---|------------------|--|--|
| <b>Non-serious adverse events</b>                                   | Group 1: 10mg/kg |  |  |
| Total subjects affected by non-serious adverse events               |                  |  |  |
| subjects affected / exposed   | 30 / 33 (90.91%) |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |  |  |
| Tumour Pain   |                  |  |  |
| subjects affected / exposed   | 0 / 33 (0.00%)   |  |  |
| occurrences (all)   | 0                |  |  |
| Vascular disorders  |                  |  |  |
| Hypotension   |                  |  |  |
| subjects affected / exposed   | 1 / 33 (3.03%)   |  |  |
| occurrences (all)   | 1                |  |  |
| General disorders and administration site conditions                |                  |  |  |
| Asthenia  |                  |  |  |
| subjects affected / exposed   | 1 / 33 (3.03%)   |  |  |
| occurrences (all)   | 4                |  |  |
| Chest Pain  |                  |  |  |
| subjects affected / exposed   | 3 / 33 (9.09%)   |  |  |
| occurrences (all)   | 3                |  |  |
| Fatigue   |                  |  |  |
| subjects affected / exposed   | 7 / 33 (21.21%)  |  |  |
| occurrences (all)   | 8                |  |  |
| Mucosal Inflammation  |                  |  |  |
| subjects affected / exposed   | 2 / 33 (6.06%)   |  |  |
| occurrences (all)   | 7                |  |  |
| Oedema Peripheral   |                  |  |  |
| subjects affected / exposed   | 2 / 33 (6.06%)   |  |  |
| occurrences (all)   | 2                |  |  |
| Pain  |                  |  |  |
| subjects affected / exposed   | 4 / 33 (12.12%)  |  |  |
| occurrences (all)   | 4                |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| Pyrexia   |                  |  |  |
| subjects affected / exposed                     | 11 / 33 (33.33%) |  |  |
| occurrences (all)                               | 13               |  |  |
| Respiratory, thoracic and mediastinal disorders |                  |  |  |
| Cough   |                  |  |  |
| subjects affected / exposed                     | 7 / 33 (21.21%)  |  |  |
| occurrences (all)                               | 9                |  |  |
| Dyspnoea  |                  |  |  |
| subjects affected / exposed                     | 4 / 33 (12.12%)  |  |  |
| occurrences (all)                               | 4                |  |  |
| Dyspnoea Exertional                             |                  |  |  |
| subjects affected / exposed                     | 2 / 33 (6.06%)   |  |  |
| occurrences (all)                               | 2                |  |  |
| Epistaxis                                       |                  |  |  |
| subjects affected / exposed                     | 2 / 33 (6.06%)   |  |  |
| occurrences (all)                               | 5                |  |  |
| Haemoptysis                                     |                  |  |  |
| subjects affected / exposed                     | 2 / 33 (6.06%)   |  |  |
| occurrences (all)                               | 2                |  |  |
| Oropharyngeal Pain                              |                  |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Pleural Effusion                                |                  |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Pneumothorax                                    |                  |  |  |
| subjects affected / exposed                     | 2 / 33 (6.06%)   |  |  |
| occurrences (all)                               | 3                |  |  |
| Rhinorrhoea                                     |                  |  |  |
| subjects affected / exposed                     | 5 / 33 (15.15%)  |  |  |
| occurrences (all)                               | 10               |  |  |
| Wheezing  |                  |  |  |
| subjects affected / exposed                     | 0 / 33 (0.00%)   |  |  |
| occurrences (all)                               | 0                |  |  |
| Psychiatric disorders                           |                  |  |  |

|  |                       |  |  |
|--|-----------------------|--|--|
| Anxiety<br>subjects affected / exposed<br>occurrences (all)  | 3 / 33 (9.09%)<br>3   |  |  |
| Depression<br>subjects affected / exposed<br>occurrences (all)   | 3 / 33 (9.09%)<br>4   |  |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)   | 3 / 33 (9.09%)<br>4   |  |  |
| Investigations<br>Aspartate Aminotransferase*<br>Increased<br>subjects affected / exposed<br>occurrences (all)           | 0 / 33 (0.00%)<br>0   |  |  |
| Blood Alkaline Phosphatase*<br>Increased<br>subjects affected / exposed<br>occurrences (all)                             | 2 / 33 (6.06%)<br>2   |  |  |
| Gamma-Glutamyltransferase*<br>Increased<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 33 (3.03%)<br>1   |  |  |
| Haemoglobin Decreased<br>subjects affected / exposed<br>occurrences (all)  | 6 / 33 (18.18%)<br>12 |  |  |
| Platelet Count Decreased<br>subjects affected / exposed<br>occurrences (all)   | 1 / 33 (3.03%)<br>1   |  |  |
| Weight Decreased<br>subjects affected / exposed<br>occurrences (all)   | 1 / 33 (3.03%)<br>1   |  |  |
| Injury, poisoning and procedural complications<br>Incision Site Pain<br>subjects affected / exposed<br>occurrences (all) | 2 / 33 (6.06%)<br>2   |  |  |
| Post Procedural Haemorrhage  |                       |  |  |

|   |   |  |  |
|---|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Post-Thoracotomy Pain Syndrome</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Procedural Pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>1 / 33 (3.03%)</p> <p>1</p> <p>1 / 33 (3.03%)</p> <p>1</p> <p>6 / 33 (18.18%)</p> <p>7</p> |  |  |
| <p>Cardiac disorders</p> <p>Tachycardia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Sinus Tachycardia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>1 / 33 (3.03%)</p> <p>1</p> <p>1 / 33 (3.03%)</p> <p>1</p>                                 |  |  |
| <p>Nervous system disorders</p> <p>Dizziness</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Headache</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Somnolence</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                      | <p>1 / 33 (3.03%)</p> <p>1</p> <p>7 / 33 (21.21%)</p> <p>8</p> <p>1 / 33 (3.03%)</p> <p>1</p> |  |  |
| <p>Blood and lymphatic system disorders</p> <p>Anaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Thrombocytopenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Leukopenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Neutropenia</p> | <p>2 / 33 (6.06%)</p> <p>3</p> <p>0 / 33 (0.00%)</p> <p>0</p> <p>2 / 33 (6.06%)</p> <p>2</p>  |  |  |

|  |                        |  |  |
|--|------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 33 (3.03%)<br>1    |  |  |
| Ear and labyrinth disorders<br>Tinnitus<br>subjects affected / exposed<br>occurrences (all)      | 3 / 33 (9.09%)<br>3    |  |  |
| Gastrointestinal disorders<br>Abdominal Pain<br>subjects affected / exposed<br>occurrences (all) | 3 / 33 (9.09%)<br>3    |  |  |
| Abdominal Pain Upper<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 33 (0.00%)<br>0    |  |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                 | 9 / 33 (27.27%)<br>10  |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                    | 6 / 33 (18.18%)<br>11  |  |  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 33 (3.03%)<br>2    |  |  |
| Gastrooesophageal Reflux*<br>Disease<br>subjects affected / exposed<br>occurrences (all)         | 0 / 33 (0.00%)<br>0    |  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                                       | 12 / 33 (36.36%)<br>18 |  |  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)                                   | 1 / 33 (3.03%)<br>1    |  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                     | 8 / 33 (24.24%)<br>9   |  |  |
| Skin and subcutaneous tissue disorders   |                        |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Alopecia<br>subjects affected / exposed<br>occurrences (all)<br><br>Pruritus<br>subjects affected / exposed<br>occurrences (all)<br><br>Rash<br>subjects affected / exposed<br>occurrences (all)<br><br>Subcutaneous Emphysema<br>subjects affected / exposed<br>occurrences (all)<br><br>Urticaria<br>subjects affected / exposed<br>occurrences (all) | 2 / 33 (6.06%)  |  |  |
|   | 2               |  |  |
|   | 4 / 33 (12.12%) |  |  |
|   | 6               |  |  |
|   | 2 / 33 (6.06%)  |  |  |
|   | 2               |  |  |
| 0 / 33 (0.00%)  | 0               |  |  |
|   | 0               |  |  |
| 0 / 33 (0.00%)  | 0 / 33 (0.00%)  |  |  |
|   | 0               |  |  |
| Renal and urinary disorders   |                 |  |  |
| Dysuria   |                 |  |  |
| subjects affected / exposed   | 0 / 33 (0.00%)  |  |  |
| occurrences (all)   | 0               |  |  |
| Musculoskeletal and connective tissue disorders   |                 |  |  |
| Arthralgia  |                 |  |  |
| subjects affected / exposed   | 2 / 33 (6.06%)  |  |  |
| occurrences (all)   | 4               |  |  |
| Bone Pain   |                 |  |  |
| subjects affected / exposed   | 1 / 33 (3.03%)  |  |  |
| occurrences (all)   | 1               |  |  |
| Back Pain   |                 |  |  |
| subjects affected / exposed   | 4 / 33 (12.12%) |  |  |
| occurrences (all)   | 4               |  |  |
| Muscle Spasms   |                 |  |  |
| subjects affected / exposed   | 3 / 33 (9.09%)  |  |  |
| occurrences (all)   | 6               |  |  |
| Flank Pain  |                 |  |  |
| subjects affected / exposed   | 0 / 33 (0.00%)  |  |  |
| occurrences (all)   | 0               |  |  |
| Muscular Weakness   |                 |  |  |

|                                    |                 |  |  |
|------------------------------------|-----------------|--|--|
| subjects affected / exposed        | 0 / 33 (0.00%)  |  |  |
| occurrences (all)                  | 0               |  |  |
| Musculoskeletal Chest Pain         |                 |  |  |
| subjects affected / exposed        | 2 / 33 (6.06%)  |  |  |
| occurrences (all)                  | 2               |  |  |
| Musculoskeletal Pain               |                 |  |  |
| subjects affected / exposed        | 2 / 33 (6.06%)  |  |  |
| occurrences (all)                  | 2               |  |  |
| Myalgia                            |                 |  |  |
| subjects affected / exposed        | 0 / 33 (0.00%)  |  |  |
| occurrences (all)                  | 0               |  |  |
| Neck Pain                          |                 |  |  |
| subjects affected / exposed        | 0 / 33 (0.00%)  |  |  |
| occurrences (all)                  | 0               |  |  |
| Pain In Extremity                  |                 |  |  |
| subjects affected / exposed        | 4 / 33 (12.12%) |  |  |
| occurrences (all)                  | 8               |  |  |
| Pain In Jaw                        |                 |  |  |
| subjects affected / exposed        | 0 / 33 (0.00%)  |  |  |
| occurrences (all)                  | 0               |  |  |
| Infections and infestations        |                 |  |  |
| Bronchitis                         |                 |  |  |
| subjects affected / exposed        | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Nasopharyngitis                    |                 |  |  |
| subjects affected / exposed        | 2 / 33 (6.06%)  |  |  |
| occurrences (all)                  | 2               |  |  |
| Rhinitis                           |                 |  |  |
| subjects affected / exposed        | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Sinusitis                          |                 |  |  |
| subjects affected / exposed        | 0 / 33 (0.00%)  |  |  |
| occurrences (all)                  | 0               |  |  |
| Upper Respiratory Tract* Infection |                 |  |  |
| subjects affected / exposed        | 3 / 33 (9.09%)  |  |  |
| occurrences (all)                  | 4               |  |  |



|   |                      |  |  |
|---|----------------------|--|--|
| Urinary Tract Infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 33 (0.00%)<br>0  |  |  |
| Metabolism and nutrition disorders  |                      |  |  |
| Decreased Appetite<br>subjects affected / exposed<br>occurrences (all)      | 4 / 33 (12.12%)<br>5 |  |  |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)             | 0 / 33 (0.00%)<br>0  |  |  |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)          | 3 / 33 (9.09%)<br>6  |  |  |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all)        | 3 / 33 (9.09%)<br>3  |  |  |
| Hypocalcaemia<br>subjects affected / exposed<br>occurrences (all)           | 0 / 33 (0.00%)<br>0  |  |  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)            | 2 / 33 (6.06%)<br>3  |  |  |
| Hyponatraemia<br>subjects affected / exposed<br>occurrences (all)           | 2 / 33 (6.06%)<br>2  |  |  |
| Hypophosphataemia<br>subjects affected / exposed<br>occurrences (all)       | 2 / 33 (6.06%)<br>2  |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment   |
|----------------|---|
| 28 March 2008  | Inclusion criteria were modified to permit a wider selection of previous chemotherapy regimens for Groups 1 and 2. Study objectives were modified and overall survival for all groups added. For subjects relapsing after treatment with SCH 717454 at 0.3 mg/kg IV not eligible for surgical resection, consideration for treatment with 10 mg/kg IV was to be discussed with the Sponsor. |
| 18 June 2008   | Response criteria were modified because of characteristics of osteosarcoma tumors (significant matrix); participants with disease after resection could remain on study treatment; observation of participants post-treatment could be adjusted for state and local regulations.  |
| 17 April 2009  | Allowed younger participants to be enrolled.  |
| 17 August 2011 | The primary reason for amendment is to discontinue protocol-specific procedures that fall outside of the standard-of-care and to stop data collection except for SAE reports.   |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

The study was stopped prematurely for administrative reasons; not all planned endpoints were analyzed.

Notes: