

**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**

The data reported in v3 is not correct and has been removed from public view

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	v2
This version publication date	16 March 2016
First version publication date	13 June 2015
Version creation reason	<ul style="list-style-type: none">• Correction of full data set Corrections to approval dates of substantial amendments

Trial information**Trial identification**

Sponsor protocol code	P04720
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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., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., 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	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
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
Worldwide total number of subjects	219
EEA total number of subjects	57

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	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 ≥ 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
Arm title	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 (± 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.

Arm title	Group 1: 10 mg/kg
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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 (± 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.

Arm title	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.

Arm title	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.

Number of subjects in period 1	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
Not treated	1	-	1
Protocol deviation	2	1	-
Lack of efficacy	23	26	30

Number of subjects in period 1	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
Not treated	1
Protocol deviation	-
Lack of efficacy	97

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	± 11.4	-	
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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: 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.	

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) ^{[1][2]}
End point description: Response to therapy achieved by study participants in Group 3, confirmed by central review	
End point type	Primary
End point timeframe: 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: Justification: This analysis was only planned for Group 3 participants.

End point values	Group 3: 10 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	84 ^[3]			
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) ^{[4][5]}
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End point description:

Response to treatment confirmed by central review for participants in Group 2.

End point type	Primary
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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 ^[6]			
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
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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
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End point timeframe:

Up to 2 years

End point values	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

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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.0
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Reporting groups

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

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

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

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

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

subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	0 / 115 (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
Metastases To Lung			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 115 (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
Tumour Pain			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	3 / 115 (2.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 115 (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
Haemorrhage			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock Haemorrhagic			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 115 (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 / 34 (0.00%)	0 / 115 (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%)	0 / 34 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound Treatment			

subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 115 (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
Thoracotomy			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 115 (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%)	0 / 34 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest Pain			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	4 / 115 (3.48%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device Dislocation			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 115 (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
Condition Aggravated			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 115 (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
Fatigue			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug Withdrawal Syndrome			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthermia			

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

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

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

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

complications			
Brain Herniation			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Humerus Fracture			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 115 (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
Postoperative Respiratory* Distress			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 115 (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%)	1 / 34 (2.94%)	0 / 115 (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
Rib Fracture			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity To Various Agents			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound Necrosis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	0 / 115 (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%)	0 / 34 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 115 (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
Cardiac Failure			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardio-Respiratory Arrest			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Altered State Of Consciousness			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coma			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Convulsion			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			

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

subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	2 / 115 (1.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic Encephalopathy			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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%)	0 / 34 (0.00%)	3 / 115 (2.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile Neutropenia			
subjects affected / exposed	2 / 34 (5.88%)	0 / 34 (0.00%)	0 / 115 (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
Febrile Bone Marrow Aplasia			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	4 / 115 (3.48%)
occurrences causally related to treatment / all	0 / 0	2 / 2	3 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Blindness Unilateral			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vision Blurred			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

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

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

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

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

subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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%)	0 / 34 (0.00%)	2 / 115 (1.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	0 / 115 (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

Serious adverse events	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		
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		
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		
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			
Hypotension			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhage			
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		
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		
Thoracotomy			
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		
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		
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		
Fatigue			
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		
Hyperthermia			

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			
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 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			
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		
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			
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		
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		
Insomnia			
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		
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		
Myoclonus			
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		
Syncope			
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		
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 Neutropenia			
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		
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			
Upper Gastrointestinal* Haemorrhage				
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			
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		
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		
Hypercreatinaemia			
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		
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		
Bronchopneumonia			
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		
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		
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		
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		
Sepsis			
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 %

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

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

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

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

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

subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	2 / 34 (5.88%) 2	4 / 115 (3.48%) 5
Nausea subjects affected / exposed occurrences (all)	13 / 34 (38.24%) 20	5 / 34 (14.71%) 6	35 / 115 (30.43%) 48
Vomiting subjects affected / exposed occurrences (all)	9 / 34 (26.47%) 12	3 / 34 (8.82%) 4	25 / 115 (21.74%) 40
Stomatitis subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2	0 / 34 (0.00%) 0	6 / 115 (5.22%) 6
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 34 (0.00%) 0	1 / 115 (0.87%) 1
Pruritus subjects affected / exposed occurrences (all)	6 / 34 (17.65%) 8	2 / 34 (5.88%) 2	5 / 115 (4.35%) 6
Rash subjects affected / exposed occurrences (all)	3 / 34 (8.82%) 6	1 / 34 (2.94%) 1	11 / 115 (9.57%) 12
Urticaria subjects affected / exposed occurrences (all)	3 / 34 (8.82%) 4	0 / 34 (0.00%) 0	1 / 115 (0.87%) 1
Subcutaneous Emphysema subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2	0 / 34 (0.00%) 0	1 / 115 (0.87%) 1
Renal and urinary disorders			
Dysuria subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	3 / 34 (8.82%) 3	2 / 115 (1.74%) 3
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	4 / 34 (11.76%) 4	3 / 34 (8.82%) 3	10 / 115 (8.70%) 12
Bone Pain			

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

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

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

Non-serious adverse events	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		
Fatigue			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	8		
Chest Pain			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
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		
Wheezing			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	10		
Psychiatric disorders			

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

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

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

Alopecia subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all) Subcutaneous Emphysema subjects affected / exposed occurrences (all)	2 / 33 (6.06%)		
	2		
	4 / 33 (12.12%)		
	6		
	2 / 33 (6.06%)		
	2		
	0 / 33 (0.00%)		
	0		
	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		
Flank Pain			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Muscle Spasms			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	6		
Muscular Weakness			

subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Myalgia			
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		
Pain In Extremity			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	8		
Neck Pain			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
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		
Sinusitis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Urinary Tract Infection			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		

Upper Respiratory Tract* Infection subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 4		
Metabolism and nutrition disorders			
Decreased Appetite subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 5		
Hyperglycaemia subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 6		
Dehydration subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0		
Hypocalcaemia subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3		
Hypokalaemia subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 3		
Hypophosphataemia subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Hyponatraemia subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 May 2008	AM1: 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.
01 August 2008	AM2: 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.
01 May 2009	AM3: Allowed younger participants to be enrolled.
08 December 2010	AM4: Changes to vial fill and drug supply.
14 September 2011	AM5: 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:

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: