Clinical trial results:
A CCLG/Cancer Research UK Phase I Trial of AT9283 (a selective inhibitor of aurora kinases) given for 72 hours every 21 days via intravenous infusion in children and adolescents with relapsed and refractory solid tumours

Summary

EudraCT number	2008-005542-23
Trial protocol	GB
Global end of trial date	30 August 2019
Results information	
Result version number	v2 (current)
This version publication date	13 March 2020
First version publication date	15 April 2017
Version creation reason	• New data added to full data set Additional data through to end of trial for patient who remained on long term treatment. This patient is now off study and the trial is closed.

Trial information

Trial identification	
Sponsor protocol code	CR0708-11
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00985868
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Cancer Research UK
Sponsor organisation address	2 Redman Place, London, United Kingdom, E20 1JQ
Public contact	Centre for Drug Development, Cancer Research UK, +44 2072420200, regulatory@cancer.org.uk
Scientific contact	Centre for Drug Development, Cancer Research UK, +44 2072420200, regulatory@cancer.org.uk

Notes:

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 August 2019
Global end of trial reached?	Yes
Global end of trial date	30 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of AT9283 (given by intravenous [IV] infusion) by characterising the dose limiting toxicities (DLTs) and determining a maximum tolerated dose (MTD) in children and adolescents with relapsed and refractory solid tumours.

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 October 2009
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	United Kingdom: 33
Worldwide total number of subjects	33
EEA total number of subjects	33

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)	21
Adolescents (12-17 years)	10
Adults (18-64 years)	2
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

For the overall trial participants were enrolled from 20 October 2009 to 31 December 2012 in five clinical trial centres in the UK.

Pre-assignment

Screening details:

Males or females aged 2-18 years with histologically proven solid tumours refractory to conventional treatment, or for which no conventional therapy existed. Patients had to have no prior exposure to an aurora kinase inhibitor, a life expectancy of at least 12 weeks and have a WHO performance status of 0-2 or Lansky Play Performance Scale ≥70%.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

AT9283 at 7.0 mg/m2

Arm type	Experimental
Investigational medicinal product name	AT9283
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

AT9283 was administered as an IV infusion over 72 hours by central line. One cycle of treatment was defined as a 72 hour (Days 1-3) IV infusion of AT9283 every 21 days.

Arm title	Cohort 2

Arm description:

AT9283 at 9.0 mg/m2

Arm type	Experimental
Investigational medicinal product name	AT9283
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

AT9283 was administered as an IV infusion over 72 hours by central line. One cycle of treatment was defined as a 72 hour (Days 1-3) IV infusion of AT9283 every 21 days.

Arm title	Cohort 3

Arm description:

AT9283 at 11.5 mg/m2

Arm type	Experimental

Investigational medicinal product name	AT9283
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

AT9283 was administered as an IV infusion over 72 hours by central line. One cycle of treatment was defined as a 72 hour (Days 1-3) IV infusion of AT9283 every 21 days.

Arm title	Cohort 4

Arm description:

AT9283 at 14.5 mg/m2

Arm type	Experimental
Investigational medicinal product name	AT9283
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

AT9283 was administered as an IV infusion over 72 hours by central line. One cycle of treatment was defined as a 72 hour (Days 1-3) IV infusion of AT9283 every 21 days.

Arm title	Cohort 5

Arm description:

AT9283 at 18.5 mg/m2

Arm type	Experimental
Investigational medicinal product name	AT9283
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

AT9283 was administered as an IV infusion over 72 hours by central line. One cycle of treatment was defined as a 72 hour (Days 1-3) IV infusion of AT9283 every 21 days.

Arm title	Cohort 6

Arm description:

AT9283 at 23.0 mg/m2

Arm type	Experimental
Investigational medicinal product name	AT9283
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

AT9283 was administered as an IV infusion over 72 hours by central line. One cycle of treatment was defined as a 72 hour (Days 1-3) IV infusion of AT9283 every 21 days.

Number of subjects in period 1	Cohort 1	Cohort 2	Cohort 3
Started	6	5	6
Completed	6	5	6

Number of subjects in period 1	Cohort 4	Cohort 5	Cohort 6
Started	7	7	2
Completed	7	7	2

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1
Reporting group description: AT9283 at 7.0 mg/m2	
Reporting group title	Cohort 2
Reporting group description: AT9283 at 9.0 mg/m2	
Reporting group title	Cohort 3
Reporting group description: AT9283 at 11.5 mg/m2	
Reporting group title	Cohort 4
Reporting group description: AT9283 at 14.5 mg/m2	
Reporting group title	Cohort 5
Reporting group description: AT9283 at 18.5 mg/m2	
Reporting group title	Cohort 6
Reporting group description: AT9283 at 23.0 mg/m2	

Reporting group values	Cohort 1	Cohort 2	Cohort 3
Number of subjects	6	5	6
Age categorical Units: Subjects			
Children (2-11 years)	4	3	4
Adolescents (12-17 years)	2	2	2
Adults (18-64 years)	0	0	0
Gender categorical Units: Subjects			
Female	3	3	5
Male	3	2	1

Reporting group values	Cohort 4	Cohort 5	Cohort 6
Number of subjects	7	7	2
Age categorical Units: Subjects			
Children (2-11 years)	6	3	1
Adolescents (12-17 years)	1	2	1
Adults (18-64 years)	0	2	0
Gender categorical Units: Subjects			
Female	5	5	1
Male	2	2	1

Reporting group values	Total		
Number of subjects	33		

Age categorical Units: Subjects			
Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years)	21 10 2		
Gender categorical Units: Subjects			
Female Male	22 11		

Subject analysis sets	
Subject analysis set title	Overall Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: All enrolled patients for the overall trial who received at least one infusion of AT9283.	
Subject analysis set title	Response Population
Subject analysis set type	Sub-group analysis
Subject analysis set description: All eligible patients who received AT9283, had measureable disease at baseline according to RECIST criteria (or according to the International Neuroblastoma Response Criteria [INRC] for neuroblastoma patients), and had a second radiological tumour assessment.	
Subject analysis set title	Pharmacokinetic Population
Subject analysis set type	Sub-group analysis
Subject analysis set description: All eligible patients who received at least one infusion of AT9283 and provided pre- and post-infusion pharmacokinetic plasma samples.	
Subject analysis set title	Pharmacodynamic Population (ELISA)
Subject analysis set type	Sub-group analysis
Subject analysis set description: All eligible patients who received at least one infusion of AT9283 and provided pre- and post-infusion pharmacodynamic blood samples during Cycle 1.	

Reporting group values	Overall Safety Population	Response Population	Pharmacokinetic Population
Number of subjects	33	22	32
Age categorical Units: Subjects			
Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years)	21 10 2	11 9 2	20 10 2
Gender categorical Units: Subjects			
Female Male	22 11	14 8	22 10

Reporting group values	Pharmacodynamic Population (ELISA)		
Number of subjects	32		
Age categorical Units: Subjects			
Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years)	20 10 2		

Gender categorical Units: Subjects			
Female	22		
Male	10		

End points

End points reporting groups

Reporting group title	Cohort 1
Reporting group description: AT9283 at 7.0 mg/m2	
Reporting group title	Cohort 2
Reporting group description: AT9283 at 9.0 mg/m2	
Reporting group title	Cohort 3
Reporting group description: AT9283 at 11.5 mg/m2	
Reporting group title	Cohort 4
Reporting group description: AT9283 at 14.5 mg/m2	
Reporting group title	Cohort 5
Reporting group description: AT9283 at 18.5 mg/m2	
Reporting group title	Cohort 6
Reporting group description: AT9283 at 23.0 mg/m2	
Subject analysis set title	Overall Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: All enrolled patients for the overall trial who received at least one infusion of AT9283.	
Subject analysis set title	Response Population
Subject analysis set type	Sub-group analysis
Subject analysis set description: All eligible patients who received AT9283, had measureable disease at baseline according to RECIST criteria (or according to the International Neuroblastoma Response Criteria [INRC] for neuroblastoma patients), and had a second radiological tumour assessment.	
Subject analysis set title	Pharmacokinetic Population
Subject analysis set type	Sub-group analysis
Subject analysis set description: All eligible patients who received at least one infusion of AT9283 and provided pre- and post-infusion pharmacokinetic plasma samples.	
Subject analysis set title	Pharmacodynamic Population (ELISA)
Subject analysis set type	Sub-group analysis
Subject analysis set description: All eligible patients who received at least one infusion of AT9283 and provided pre- and post-infusion pharmacodynamic blood samples during Cycle 1.	

Primary: Safety

End point title	Safety[1]

End point description:

The causality and severity grading of each adverse event (AE) to AT9283, according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. AEs with a causality of possibly, probably or almost certainly related to AT9283 were considered to indicate relatedness.
Dose limiting toxicity was defined as almost certainly or probably related to AT9283 and when one or more of the following occurred:
a) CTCAE Grade 3 or higher non-haematological toxicity excluding:
- Grade 3 nausea and vomiting in patients who had not received optimal treatment with anti-emetics.
- Grade 3 fever in the absence of Grade 3 or 4 neutropenia.

- Grade 3 transaminase elevations that reversed to ≤Grade 1 before Day 22.
- Grade 3 diarrhoea in patients who had not received optimal treatment with anti-diarrhoeals.

b) CTCAE Grade 4 neutropenia lasting ≥7 days.
c) CTCAE Grade 3 thrombocytopenia lasting >7 days or any Grade 4 thrombocytopenia.

End point type	Primary

End point timeframe:

From patient consent to 28 days post last administration of AT9283.

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: All safety data were presented in a descriptive fashion, with AEs presented by CTCAE adverse event term by worst grade observed.

End point values	Overall Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: Number of AEs				
All AEs	675			
Related AEs	235			
DLT - neutropenia	3			
DLT - febrile neutropenia	2			
DLT - suspected bacterial infection	1			

Attachments (see zip file)	AT9283 DLT Summary_CSR extract_prepared 30Mar17.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Tumour Response

End point title	Tumour Response

End point description:

All eligible patients who received AT9283, had measurable disease at baseline according to Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.0 and had a second radiological tumour assessment were evaluable for response. For neuroblastoma patients, response was assessed according to the International Neuroblastoma Response Criteria (INRC).
Patients with measureable disease were placed into response categories of complete response (CR), partial response (PR), stable disease (SD), progressive disease and early progression. Very good partial response, mixed response and no response were also included for patients assessed using INRC.
For responses of CR and PR, changes in tumour measurements were required to be confirmed by repeat assessments performed no less than four weeks after the response criteria were initially met. For SD, tumour measurements were required to have met the criteria for SD at least once and at a minimum of six weeks after AT9283 was started.

End point type	Secondary

End point timeframe:

From baseline assessment and then after every two cycles until 28 days post last administration of AT9283.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	4	4
Units: Number of patients				
number (not applicable)				
Complete Response	0	0	0	0
Partial Response	0	0	0	0
Stable Disease	1	2	1	2
Progressive Disease	3	0	2	2
Early Progression	0	0	0	0
Very good Partial Response (INRC)	0	0	0	0
Mixed Response (INRC)	0	0	1	0
No Response (INRC)	0	1	0	0

End point values	Cohort 5	Cohort 6	Response Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	5	2	22	
Units: Number of patients				
number (not applicable)				
Complete Response	0	0	0	
Partial Response	1	0	1	
Stable Disease	2	0	8	
Progressive Disease	2	2	11	
Early Progression	0	0	0	
Very good Partial Response (INRC)	0	0	0	
Mixed Response (INRC)	0	0	1	
No Response (INRC)	0	0	1	

Attachments (see zip file)	AT9283 Tumour Marker Summary_CSR extract_prepared

Statistical analyses

No statistical analyses for this end point

Secondary: AT9283 Pharmacokinetic Profile

End point title	AT9283 Pharmacokinetic Profile

End point description:

Pharmacokinetic parameters estimated included area under the plasma concentration-time curve (AUC); maximum concentration achieved (Cmax); time to maximum concentration (Tmax); elimination half-life (T1/2); clearance (Cl) and volume of distribution at steady state (Vss) for AT9283.

End point type	Secondary

End point timeframe:

Pre-treatment (during screening within one week prior to first AT9283 administration), 4, 24, 48, 70, 73, 76 and 96 hours post infusion in Cycle 1 only.

End point values	Pharmacokinetic Population			
Subject group type	Subject analysis set			
Number of subjects analysed	32			
Units: Number of patients				
number (not applicable)				
Dose Level 7.0 mg/m2	5			
Dose Level 9.0 mg/m2	5			
Dose Level 11.5 mg/m2	6			
Dose Level 14.5 mg/m2	7			
Dose Level 18.5 mg/m2	7			
Dose Level 23.0 mg/m2	2			

Attachments (see zip file)	AT9283 PK Summary_CSR extract_prepared 30Mar17.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamic Activity of AT9283

End point title	Pharmacodynamic Activity of AT9283

End point description:

Investigation of the pharmacodynamic behaviour of AT9283 using enzyme linked immunosorbent assays to analyse levels of circulating cytokeratin 18 (M65 ELISA) and caspase 3 cleaved cytokeratin 18 (M30 ELISA) in plasma as surrogate markers for cell death and apoptosis respectively.

End point type	Secondary

End point timeframe:

Pre-treatment (within one week prior to first AT9283 administration), then at 24 hours, 48 hours, 70 hours and 8 days post-infusion during Cycle 1 only.

End point values	Pharmacodynamic Population (ELISA)			
Subject group type	Subject analysis set			
Number of subjects analysed	32			
Units: Number of patients				
number (not applicable)				
Dose Level 7.0 mg/m2	5			
Dose Level 9.0 mg/m2	5			
Dose Level 11.5 mg/m2	6			
Dose Level 14.5 mg/m2	7			
Dose Level 18.5 mg/m2	7			
Dose Level 23.0 mg/m2	2			

Attachments (see zip file)	AT9283 PD Summary_CSR extract_prepared 30Mar17.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of consent until 28 days post final administration of AT9283. Any AT9283-related AEs still present at that time, were followed up monthly until the AE resolved, stabilised or the patient commenced another anti-cancer therapy.

Adverse event reporting additional description:

All eligible patients who received at least one infusion of AT9283 were included in the safety analysis. NCI CTCAE Version 3.0 was used to code AEs and grade their severity.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Cohort 1
Reporting group description: Dose Level 7.0 mg/m2	
Reporting group title	Cohort 2
Reporting group description: Dose Level 9.0 mg/m2	
Reporting group title	Cohort 3
Reporting group description: Dose Level 11.5 mg/m2	
Reporting group title	Cohort 4
Reporting group description: Dose Level 14.5 mg/m2	
Reporting group title	Cohort 5
Reporting group description: Dose Level 18.5 mg/m2	
Reporting group title	Cohort 6
Reporting group description: Dose Level 23.0 mg/m2	
Reporting group title	Overall Safety Population

Reporting group description: -

Serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	2 / 5 (40.00%)	4 / 6 (66.67%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Somnolence			

subjects affected / exposed	3 / 6 (50.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	3 / 6 (50.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (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
Neurology - other			
subjects affected / exposed	1 / 6 (16.67%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pain - head/headache			
subjects affected / exposed	2 / 6 (33.33%)	0 / 5 (0.00%)	0 / 6 (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
Tremor			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 6 (16.67%)	1 / 5 (20.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	1 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (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
Death - disease progression			

subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pain - other			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (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
Injection site reaction			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Haemorrhage - other			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (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
Neutrophils			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (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
Immune system disorders			
Allergic reaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (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
Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (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 GI - oral cavity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (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
Reproductive system and breast disorders			
Reproductive system - other (infertility/sterility)			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (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
Skin and subcutaneous tissue disorders			
Hand-foot			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscle weakness left-sided			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (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
Muscle weakness right-sided			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (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
Pain - back			

subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (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 - bone			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (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 - joint			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (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 - chest wall			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infection - other			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection normal ANC - soft tissue NOS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
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 DC - upper airway NOS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (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

Serious adverse events	Cohort 4	Cohort 5	Cohort 6
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	5 / 7 (71.43%)	2 / 2 (100.00%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Somnolence			
subjects affected / exposed	0 / 7 (0.00%)	3 / 7 (42.86%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	0 / 2 (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
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (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
Neurology - other			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain - head/headache			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (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 disorders and administration site conditions			
Fever			

subjects affected / exposed	1 / 7 (14.29%)	3 / 7 (42.86%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (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
Death - disease progression			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (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
Pain - other			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (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
Injection site reaction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Haemorrhage - other			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (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
Neutrophils			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergic reaction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (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
Gastrointestinal disorders			

Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	0 / 2 (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
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage GI - oral cavity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Reproductive system - other (infertility/sterility)			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 2 (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
Skin and subcutaneous tissue disorders			
Hand-foot			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (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			

Muscle weakness left-sided			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (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
Muscle weakness right-sided			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (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
Pain - back			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (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
Pain - bone			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (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
Pain - joint			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (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
Pain - chest wall			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 2 (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
Infections and infestations			
Infection - other			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	3 / 7 (42.86%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 0	4 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection normal ANC - soft tissue			

NOS			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (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
Infection DC - upper airway NOS			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (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	Overall Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 33 (60.61%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Somnolence			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences causally related to treatment / all	1 / 10		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neurology - other			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Pain - head/headache			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

Tremor			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences causally related to treatment / all	2 / 9		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death - disease progression			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Pain - other			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injection site reaction			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Haemorrhage - other			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutrophils			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Immune system disorders			
Allergic reaction			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhage GI - oral cavity			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Reproductive system - other (infertility/sterility)			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Hand-foot			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Urinary retention			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscle weakness left-sided			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Muscle weakness right-sided			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain - back			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain - bone			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain - joint			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain - chest wall			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection - other			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		

Febrile neutropenia			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Infection normal ANC - soft tissue NOS			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection DC - upper airway NOS			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	5 / 5 (100.00%)	5 / 6 (83.33%)
Vascular disorders			
Vascular - other			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 6 (16.67%)	2 / 5 (40.00%)	1 / 6 (16.67%)
occurrences (all)	1	3	1
Sweating			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Fever			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rigors/chills			

subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oedema: head and neck			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Oedema: limb			
subjects affected / exposed	1 / 6 (16.67%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Pain - chest/thorax NOS			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pain - other			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Flu-like syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Allergic reaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Sexual - other			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pain - throat/pharynx/larynx			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pulmonary - other			
subjects affected / exposed	1 / 6 (16.67%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Cough			

subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Voice changes			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Mood - anxiety			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Mood - agitation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Confusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Investigations			
Weight loss			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Weight gain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Intraop injury - other			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Cardiac disorders			
Hypertension			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Hypotension			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Supr - sinus bradycardia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Cardiac general - other			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cardiac arrhythmia - other			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Neuropathy - sensory			
subjects affected / exposed	1 / 6 (16.67%)	1 / 5 (20.00%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Neurology - other			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Tremor			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Ataxia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neuropathy - CN VII motor-face; sensory-taste			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Seizure			

subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Memory impairment			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neuropathy - motor			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pyramidal tract dysfunction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pain - head/headache			
subjects affected / exposed	2 / 6 (33.33%)	1 / 5 (20.00%)	2 / 6 (33.33%)
occurrences (all)	3	2	4
Pain - neuralgia/peripheral nerve			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Neutrophils			
subjects affected / exposed	1 / 6 (16.67%)	1 / 5 (20.00%)	1 / 6 (16.67%)
occurrences (all)	3	1	2
Leucocytes			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	3 / 6 (50.00%)
occurrences (all)	2	0	4
Platelets			
subjects affected / exposed	2 / 6 (33.33%)	1 / 5 (20.00%)	3 / 6 (50.00%)
occurrences (all)	2	2	5
Haemoglobin			
subjects affected / exposed	0 / 6 (0.00%)	3 / 5 (60.00%)	2 / 6 (33.33%)
occurrences (all)	0	4	3
Lymphopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	3
Blood - other			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

Haemorrhage - other			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Haemorrhage pulmonary upper respiratory - nose			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haemorrhage genitorurinary - NOS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haematoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Ocular - other			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Diplopia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nystagmus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Optic disc oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blurred vision			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eyelid dysfunction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	3 / 6 (50.00%)	2 / 5 (40.00%)	2 / 6 (33.33%)
occurrences (all)	4	2	2
Dehydration			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Mucositis (functional/symptomatic) - oral cavity			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Mucositis (clinical exam) - oral cavity			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	2 / 6 (33.33%)	2 / 5 (40.00%)	1 / 6 (16.67%)
occurrences (all)	2	2	1
Vomiting			
subjects affected / exposed	4 / 6 (66.67%)	3 / 5 (60.00%)	2 / 6 (33.33%)
occurrences (all)	6	4	4
Anorexia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Distension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dysphagia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Taste alteration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Heartburn			

subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pain - abdomen NOS			
subjects affected / exposed	2 / 6 (33.33%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	3	0	1
Pain - dental/teeth/peridontal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pain - stomach			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pain - oral cavity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hepatic - other			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	2 / 6 (33.33%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Alopecia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Striae			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dermatology - other			

subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Bruising			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cheilitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site reaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Incontinence urinary			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Urinary retention			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Urinary frequency			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Endocrine - other			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Cushingoid			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Adrenal insufficiency			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hot flashes			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

Pain - joint			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Pain - back			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pain - extremity-limb			
subjects affected / exposed	0 / 6 (0.00%)	2 / 5 (40.00%)	0 / 6 (0.00%)
occurrences (all)	0	5	0
Pain - bone			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Pain - muscle			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pain - neck			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Muscle weakness - extremity-upper			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Muscle weakness - left-sided			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Muscle weakness - facial			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal - other			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Infection normal ANC - upper airway NOS			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Infection - other			

subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	2
Infection normal ANC - catheter-related			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Infection documented clinically - wound			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Infection unknown ANC - trachea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Infection documented clinically - upper airway NOS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infection normal ANC - brain (encephalitis infectious)			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infection normal ANC - conjunctiva			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
ALT			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	1 / 6 (16.67%)
occurrences (all)	0	1	4
Bilirubin			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
GGT			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			

subjects affected / exposed	0 / 6 (0.00%)	2 / 5 (40.00%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Hypoglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypocalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypomagnesaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	3
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Alkaline phosphatase			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
AST			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	3
Metabolic/lab - other			
subjects affected / exposed	0 / 6 (0.00%)	3 / 5 (60.00%)	1 / 6 (16.67%)
occurrences (all)	0	3	2
Hyperkalaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypernatraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 4	Cohort 5	Cohort 6
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	7 / 7 (100.00%)	2 / 2 (100.00%)
Vascular disorders			
Vascular - other			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 7 (57.14%)	3 / 7 (42.86%)	1 / 2 (50.00%)
occurrences (all)	4	4	1
Sweating			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Fever			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	1 / 2 (50.00%)
occurrences (all)	1	3	1
Rigors/chills			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Oedema: head and neck			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Oedema: limb			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Pain - chest/thorax NOS			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Pain - other			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	0 / 2 (0.00%)
occurrences (all)	2	2	0
Flu-like syndrome			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	7	0
Immune system disorders			

Allergic reaction			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Reproductive system and breast disorders			
Sexual - other			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Pain - throat/pharynx/larynx			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	2	9	0
Pulmonary - other			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Cough			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	2	1	0
Voice changes			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Dyspnoea			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Mood - anxiety			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Mood - agitation			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	1	1	0

Confusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Investigations			
Weight loss			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Weight gain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Injury, poisoning and procedural complications			
Intraop injury - other			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Supr - sinus bradycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cardiac general - other			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Cardiac arrhythmia - other			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
Neuropathy - sensory			
subjects affected / exposed	0 / 7 (0.00%)	3 / 7 (42.86%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Neurology - other			

subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	1	3	0
Tremor			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Ataxia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	2 / 2 (100.00%)
occurrences (all)	2	1	2
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 2 (50.00%)
occurrences (all)	0	2	1
Somnolence			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Neuropathy - CN VII motor-face; sensory-taste			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Seizure			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	1	7	0
Memory impairment			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Neuropathy - motor			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Pyramidal tract dysfunction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Pain - head/headache			
subjects affected / exposed	3 / 7 (42.86%)	5 / 7 (71.43%)	2 / 2 (100.00%)
occurrences (all)	7	16	4
Pain - neuralgia/peripheral nerve			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Blood and lymphatic system disorders			
Neutrophils			
subjects affected / exposed	3 / 7 (42.86%)	4 / 7 (57.14%)	2 / 2 (100.00%)
occurrences (all)	3	24	3
Leucocytes			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	1 / 2 (50.00%)
occurrences (all)	3	19	2
Platelets			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	1 / 2 (50.00%)
occurrences (all)	0	6	1
Haemoglobin			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	2 / 2 (100.00%)
occurrences (all)	0	12	2
Lymphopenia			
subjects affected / exposed	2 / 7 (28.57%)	3 / 7 (42.86%)	1 / 2 (50.00%)
occurrences (all)	3	30	2
Blood - other			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Haemorrhage - other			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Haemorrhage pulmonary upper respiratory - nose			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Haemorrhage genitorurinary - NOS			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Haematoma			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Ocular - other			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Diplopia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Nystagmus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Optic disc oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Blurred vision			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Eyelid dysfunction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	1 / 2 (50.00%)
occurrences (all)	0	6	1
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Mucositis (functional/symptomatic) - oral cavity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Mucositis (clinical exam) - oral cavity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	0 / 2 (0.00%)
occurrences (all)	1	2	0
Vomiting			

subjects affected / exposed	1 / 7 (14.29%)	3 / 7 (42.86%)	2 / 2 (100.00%)
occurrences (all)	1	3	5
Anorexia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Diarrhoea			
subjects affected / exposed	1 / 7 (14.29%)	3 / 7 (42.86%)	1 / 2 (50.00%)
occurrences (all)	1	7	1
Distension			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Dysphagia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Taste alteration			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Heartburn			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Pain - abdomen NOS			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	2	8	0
Pain - dental/teeth/peridontal			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Pain - stomach			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pain - oral cavity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Hepatic - other			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 7 (0.00%)	4 / 7 (57.14%)	1 / 2 (50.00%)
occurrences (all)	0	9	1
Alopecia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	1 / 2 (50.00%)
occurrences (all)	1	2	1
Striae			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Dermatology - other			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Bruising			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Cheilitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Injection site reaction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Incontinence urinary			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Urinary retention			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Urinary frequency			

subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Endocrine - other			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cushingoid			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Adrenal insufficiency			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Hot flashes			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Pain - joint			
subjects affected / exposed	2 / 7 (28.57%)	3 / 7 (42.86%)	0 / 2 (0.00%)
occurrences (all)	2	6	0
Pain - back			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	3	2	0
Pain - extremity-limb			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	0 / 2 (0.00%)
occurrences (all)	2	4	0
Pain - bone			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pain - muscle			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Pain - neck			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Muscle weakness - extremity-upper			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Muscle weakness - left-sided			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Muscle weakness - facial			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal - other			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	6	0
Infections and infestations			
Infection normal ANC - upper airway NOS			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Infection - other			
subjects affected / exposed	4 / 7 (57.14%)	4 / 7 (57.14%)	1 / 2 (50.00%)
occurrences (all)	4	9	2
Infection normal ANC - catheter-related			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Infection documented clinically - wound			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Infection unknown ANC - trachea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Infection documented clinically - upper airway NOS			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Infection normal ANC - brain (encephalitis infectious)			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Infection normal ANC - conjunctiva			

subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	1 / 2 (50.00%)
occurrences (all)	0	12	1
ALT			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	0 / 2 (0.00%)
occurrences (all)	1	3	0
Bilirubin			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
GGT			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Hypoglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	4	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 2 (50.00%)
occurrences (all)	0	4	1
Hypocalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 2 (50.00%)
occurrences (all)	0	3	1
Hypomagnesaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Hypophosphataemia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	1 / 2 (50.00%)
occurrences (all)	2	0	1
Hyponatraemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 2 (50.00%)
occurrences (all)	0	6	3

Alkaline phosphatase			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	2
AST			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Metabolic/lab - other			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Hypernatraemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Overall Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 33 (96.97%)		
Vascular disorders			
Vascular - other			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	12 / 33 (36.36%)		
occurrences (all)	14		
Sweating			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Fever			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	5		
Rigors/chills			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		

Oedema: head and neck			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Oedema: limb			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	4		
Pain - chest/thorax NOS			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Pain - other			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	6		
Flu-like syndrome			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	7		
Immune system disorders			
Allergic reaction			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Sexual - other			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Pain - throat/pharynx/larynx			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	11		
Pulmonary - other			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Cough			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		

Voice changes			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Mood - anxiety			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Mood - agitation			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Confusion			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Investigations			
Weight loss			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Weight gain			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Intraop injury - other			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Cardiac disorders			
Hypertension			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Hypotension			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Supr - sinus bradycardia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Cardiac general - other			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Cardiac arrhythmia - other			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
Nervous system disorders			
Neuropathy - sensory			
subjects affected / exposed	6 / 33 (18.18%)		
occurrences (all)	6		
Neurology - other			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	7		
Tremor			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Ataxia			
subjects affected / exposed	6 / 33 (18.18%)		
occurrences (all)	6		
Dizziness			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Somnolence			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Neuropathy - CN VII motor-face; sensory-taste			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Seizure			

subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	8		
Memory impairment			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Neuropathy - motor			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Pyramidal tract dysfunction			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Pain - head/headache			
subjects affected / exposed	15 / 33 (45.45%)		
occurrences (all)	36		
Pain - neuralgia/peripheral nerve			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Neutrophils			
subjects affected / exposed	12 / 33 (36.36%)		
occurrences (all)	36		
Leucocytes			
subjects affected / exposed	8 / 33 (24.24%)		
occurrences (all)	30		
Platelets			
subjects affected / exposed	9 / 33 (27.27%)		
occurrences (all)	16		
Haemoglobin			
subjects affected / exposed	9 / 33 (27.27%)		
occurrences (all)	21		
Lymphopenia			
subjects affected / exposed	8 / 33 (24.24%)		
occurrences (all)	38		
Blood - other			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	4		

Haemorrhage - other			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Haemorrhage pulmonary upper respiratory - nose			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Haemorrhage genitorurinary - NOS			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Haematoma			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Eye disorders			
Dry eye			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Ocular - other			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Diplopia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Nystagmus			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Optic disc oedema			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Blurred vision			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Eyelid dysfunction			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	10 / 33 (30.30%)		
occurrences (all)	15		
Dehydration			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Mucositis (functional/symptomatic) - oral cavity			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Mucositis (clinical exam) - oral cavity			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	8 / 33 (24.24%)		
occurrences (all)	8		
Vomiting			
subjects affected / exposed	15 / 33 (45.45%)		
occurrences (all)	23		
Anorexia			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	6 / 33 (18.18%)		
occurrences (all)	10		
Distension			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Dysphagia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
Taste alteration			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Heartburn			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Pain - abdomen NOS			
subjects affected / exposed	6 / 33 (18.18%)		
occurrences (all)	14		
Pain - dental/teeth/peridontal			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Pain - stomach			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Pain - oral cavity			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hepatic - other			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	13		
Alopecia			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Striae			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Dermatology - other			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
Bruising			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
Cheilitis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	3		
Injection site reaction			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Renal and urinary disorders			
Incontinence urinary			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Urinary retention			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Urinary frequency			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Endocrine disorders			
Endocrine - other			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Cushingoid			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Adrenal insufficiency			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hot flashes			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			

Pain - joint			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	10		
Pain - back			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	6		
Pain - extremity-limb			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	11		
Pain - bone			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
Pain - muscle			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Pain - neck			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Muscle weakness - extremity-upper			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Muscle weakness - left-sided			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Muscle weakness - facial			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Musculoskeletal - other			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	6		
Infections and infestations			
Infection normal ANC - upper airway NOS			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Infection - other			

subjects affected / exposed	12 / 33 (36.36%)		
occurrences (all)	18		
Infection normal ANC - catheter-related			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Infection documented clinically - wound			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Infection unknown ANC - trachea			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Infection documented clinically - upper airway NOS			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Infection normal ANC - brain (encephalitis infectious)			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Infection normal ANC - conjunctiva			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	14		
ALT			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	9		
Bilirubin			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
GGT			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hyperglycaemia			

subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	4		
Hypoglycaemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	4		
Hypoalbuminaemia			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	6		
Hypocalcaemia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	4		
Hypomagnesaemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	6		
Hyponatraemia			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	10		
Alkaline phosphatase			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
AST			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	5		
Metabolic/lab - other			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	5		
Hyperkalaemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hypernatraemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 March 2010	Clarification of the required delay between dosing the first and second patients at any given dose level. Permission for 50 mL AT9283 infusion volume to be used for patients where necessary. Clarification that the total 72 hour infusion was to be achieved by means of three 24 hour infusions. Addition of the correct method for collecting bone marrow aspirate. Addition of details of the labelling requirements for the reconstituted investigational medicinal product (IMP). Addition of two new informed consent documents to allow for patient assent for optional biopsies. Clarification of the AE reporting period.
20 August 2010	Clarification of exclusion criterion regarding allergy/auto-immune disease. Clarification of timelines for IMP reconstitution. Update to information concerning blood sampling. Timing of the baseline echocardiogram changed from one week to two weeks prior to first administration of IMP.
08 April 2011	Restart to the trial on 08 April 2011 following a temporary halt. Updates to the inclusion criteria to allow patients with diffuse intrinsic pontine gliomas that had progressed or relapsed after first line therapy to be included without histological verification, and to clarify the minimum Lansky Play Scale Score required. Addition of a new exclusion criterion to exclude patients experiencing uncontrolled hypertension during the screening period. Amendment to the timing of urinalysis tests. Update to the collection of samples for pharmacodynamics analysis so that skin punch biopsies became mandatory. Change to Sponsor contact details.
18 June 2014	Reduction in the frequency of radiological disease assessments, echocardiogram and urinalysis evaluations from every two cycles of AT9283 to every four cycles for the one remaining patient on trial.
31 March 2016	Removal of requirement for echocardiogram evaluation. Increase in trial duration and clarification that final analysis could be conducted due to all patients completing their final visit (with the exception of one patient continuing to benefit from treatment). Clarification of data collection methods for one remaining patient on trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 September 2010	Recruitment to the trial was temporarily halted on 20 September 2010. This was as a direct result of the review of safety data from adult leukaemia studies with AT9283 and preliminary evidence of drug-related cardiac toxicity. Protocol Version 04 and 05 were not issued to trial sites as a result of the halt to the trial.	08 April 2011

Notes:

Limitations and caveats

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

Version 1 summary results comprised data up to the interim analysis cut-off of 25 January 2016 (one patient was continuing on trial in accordance with the protocol). Version 2 of the summary results comprises final data following global end of trial.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25370467