



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 | <ul style="list-style-type: none">• 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 $\geq 70\%$.

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) | 21 | | |
| Adolescents (12-17 years) | 10 | | |
| Adults (18-64 years) | 2 | | |
| Gender categorical Units: Subjects | | | |
| Female | 22 | | |
| Male | 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) | 21 | 11 | 20 |
| Adolescents (12-17 years) | 10 | 9 | 10 |
| Adults (18-64 years) | 2 | 2 | 2 |
| Gender categorical Units: Subjects | | | |
| Female | 22 | 14 | 22 |
| Male | 11 | 8 | 10 |

| Reporting group values | Pharmacodynamic Population (ELISA) | | |
|------------------------------------|------------------------------------|--|--|
| Number of subjects | 32 | | |
| Age categorical Units: Subjects | | | |
| Children (2-11 years) | 20 | | |
| Adolescents (12-17 years) | 10 | | |
| Adults (18-64 years) | 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/m ² | |
| Reporting group title | Cohort 2 |
| Reporting group description: AT9283 at 9.0 mg/m ² | |
| Reporting group title | Cohort 3 |
| Reporting group description: AT9283 at 11.5 mg/m ² | |
| Reporting group title | Cohort 4 |
| Reporting group description: AT9283 at 14.5 mg/m ² | |
| Reporting group title | Cohort 5 |
| Reporting group description: AT9283 at 18.5 mg/m ² | |
| Reporting group title | Cohort 6 |
| Reporting group description: AT9283 at 23.0 mg/m ² | |
| 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: <ul style="list-style-type: none">- 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 \leq 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 measurable 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

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|--|--------------------------------|
| End point title | AT9283 Pharmacokinetic Profile |
| End point description: Pharmacokinetic parameters estimated included area under the plasma concentration-time curve (AUC); maximum concentration achieved (C _{max}); time to maximum concentration (T _{max}); elimination half-life (T _{1/2}); clearance (Cl) and volume of distribution at steady state (V _{ss}) 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

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

| | | | |
|--|---------------------|---------------------|---------------------|
| Hypotension subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Supr - sinus bradycardia subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Cardiac general - other subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Cardiac arrhythmia - other subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Nervous system disorders | | | |
| Neuropathy - sensory subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 1 / 5 (20.00%) 1 | 1 / 6 (16.67%) 1 |
| Neurology - other subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 2 | 0 / 5 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Tremor subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Ataxia subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Somnolence subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Neuropathy - CN VII motor-face; sensory-taste subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 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 occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Haemorrhage pulmonary upper respiratory - nose subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Haemorrhage genitorurinary - NOS subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Haematoma subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Eye disorders | | | |
| Dry eye subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Ocular - other subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 2 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Diplopia subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Nystagmus subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Optic disc oedema subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Blurred vision subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Eyelid dysfunction subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 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 occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Bruising subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Cheilitis subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Injection site reaction subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Renal and urinary disorders Incontinence urinary subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 6 (0.00%) 0 |
| Urinary retention subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 6 (0.00%) 0 |
| Urinary frequency subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Endocrine disorders Endocrine - other subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 6 (0.00%) 0 |
| Cushingoid subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Adrenal insufficiency subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Hot flashes subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 6 (0.00%) 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 occurrences (all) | 1 / 7 (14.29%) 1 | 1 / 7 (14.29%) 1 | 0 / 2 (0.00%) 0 |
| Reproductive system and breast disorders Sexual - other subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 7 (14.29%) 1 | 0 / 2 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Apnoea subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 1 / 2 (50.00%) 1 |
| Pain - throat/pharynx/larynx subjects affected / exposed occurrences (all) | 2 / 7 (28.57%) 2 | 1 / 7 (14.29%) 9 | 0 / 2 (0.00%) 0 |
| Pulmonary - other subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 1 / 7 (14.29%) 1 | 0 / 2 (0.00%) 0 |
| Cough subjects affected / exposed occurrences (all) | 2 / 7 (28.57%) 2 | 1 / 7 (14.29%) 1 | 0 / 2 (0.00%) 0 |
| Voice changes subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 2 | 0 / 7 (0.00%) 0 | 0 / 2 (0.00%) 0 |
| Dyspnoea subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 1 / 7 (14.29%) 1 | 0 / 2 (0.00%) 0 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 2 / 7 (28.57%) 3 | 0 / 2 (0.00%) 0 |
| Mood - anxiety subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 7 (14.29%) 1 | 0 / 2 (0.00%) 0 |
| Mood - agitation subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 1 / 7 (14.29%) 1 | 0 / 2 (0.00%) 0 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Confusion subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 7 (14.29%) 1 | 0 / 2 (0.00%) 0 |
| Investigations Weight loss subjects affected / exposed occurrences (all) | 2 / 7 (28.57%) 2 | 0 / 7 (0.00%) 0 | 0 / 2 (0.00%) 0 |
| Weight gain subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 1 / 7 (14.29%) 1 | 0 / 2 (0.00%) 0 |
| Injury, poisoning and procedural complications Intraop injury - other subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 2 (0.00%) 0 |
| Cardiac disorders Hypertension subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 7 (14.29%) 1 | 0 / 2 (0.00%) 0 |
| Hypotension subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 2 (0.00%) 0 |
| Supr - sinus bradycardia subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 2 (0.00%) 0 |
| Cardiac general - other subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 1 / 2 (50.00%) 1 |
| Cardiac arrhythmia - other subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 7 (14.29%) 2 | 0 / 2 (0.00%) 0 |
| Nervous system disorders Neuropathy - sensory subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 3 / 7 (42.86%) 3 | 0 / 2 (0.00%) 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/periodontal | | | |
| 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 occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 7 (14.29%) 1 | 0 / 2 (0.00%) 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 occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 2 (0.00%) 0 |
| Muscle weakness - left-sided subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 2 (0.00%) 0 |
| Muscle weakness - facial subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 7 (0.00%) 0 | 0 / 2 (0.00%) 0 |
| Musculoskeletal - other subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 7 (14.29%) 6 | 0 / 2 (0.00%) 0 |
| Infections and infestations | | | |
| Infection normal ANC - upper airway NOS subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 7 (14.29%) 2 | 0 / 2 (0.00%) 0 |
| Infection - other subjects affected / exposed occurrences (all) | 4 / 7 (57.14%) 4 | 4 / 7 (57.14%) 9 | 1 / 2 (50.00%) 2 |
| Infection normal ANC - catheter- related subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 2 (0.00%) 0 |
| Infection documented clinically - wound subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 2 (0.00%) 0 |
| Infection unknown ANC - trachea subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 2 (0.00%) 0 |
| Infection documented clinically - upper airway NOS subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 7 (14.29%) 1 | 0 / 2 (0.00%) 0 |
| Infection normal ANC - brain (encephalitis infectious) subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 7 (14.29%) 1 | 0 / 2 (0.00%) 0 |
| Infection normal ANC - conjunctiva | | | |

| | | | |
|--|--------------------|---------------------|--------------------|
| subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 7 (14.29%) 1 | 0 / 2 (0.00%) 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 occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 1 / 2 (50.00%) 2 |
| AST subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 7 (14.29%) 2 | 0 / 2 (0.00%) 0 |
| Metabolic/lab - other subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 2 (0.00%) 0 |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 7 (14.29%) 1 | 0 / 2 (0.00%) 0 |
| Hypernatraemia subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 7 (14.29%) 1 | 0 / 2 (0.00%) 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 occurrences (all) | 1 / 33 (3.03%) 1 | | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) | 12 / 33 (36.36%) 14 | | |
| Sweating subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | | |
| Fever subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 5 | | |
| Rigors/chills subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | | |

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

| | | | |
|--|---------------------|--|--|
| Voice changes subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 3 | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 3 | | |
| Mood - anxiety subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | | |
| Mood - agitation subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | | |
| Confusion subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | | |
| Investigations Weight loss subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 3 | | |
| Weight gain subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 3 | | |
| Injury, poisoning and procedural complications Intraop injury - other subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | | |
| Cardiac disorders Hypertension subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 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 occurrences (all) | 1 / 33 (3.03%) 1 | | |
| Haemorrhage pulmonary upper respiratory - nose subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | | |
| Haemorrhage genitorurinary - NOS subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | | |
| Haematoma subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | | |
| Eye disorders | | | |
| Dry eye subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | | |
| Ocular - other subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 3 | | |
| Diplopia subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | | |
| Nystagmus subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | | |
| Optic disc oedema subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | | |
| Blurred vision subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | | |
| Eyelid dysfunction subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 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>