



Clinical trial results:

A phase I/II study evaluating the safety and activity of Pegylated recombinant human Arginase (BCT-100) in Relapsed/refractory cancers of Children and young adults

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2017-002762-44 |
| Trial protocol | GB IE NL |
| Global end of trial date | 22 July 2022 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 08 February 2023 |
| First version publication date | 08 February 2023 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | RG-16-040 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | ISRCTN21727048 |
| ClinicalTrials.gov id (NCT number) | NCT03455140 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | EudraCT Number : 2017-002762-44, ITCC: ITCC-062, CAS Number: MX1032 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | University of Birmingham |
| Sponsor organisation address | Edgbaston, Birmingham , United Kingdom, B15 2TT |
| Public contact | Birgit Whitman , University of Birmingham , 0044 07814 650 003, researchgovernance@contacts.bham.ac.uk |
| Scientific contact | Birgit Whitman , University of Birmingham , 0044 07814 650 003, researchgovernance@contacts.bham.ac.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 | 21 September 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 12 June 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 July 2022 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this trial are to:

- establish a safe and active dose of BCT-100 in children and young people
- evaluate if BCT-100 is effective against acute leukaemias, neuroblastoma, sarcoma and high grade glioma which have come back (relapsed) or not responded to previous treatment (refractory) as measured by disease response at 8 weeks.

In the first part, doctors will be looking for the dose of BCT-100 which is both safe and active in children and young adults. This will involve giving increasing doses of BCT-100 to patients to find the dose which does not cause significant side effects (known as dose-limiting toxicities) and completely depletes arginine levels. All the doses of BCT-100 used in this trial have found to be safe in adults.

In the second part the trial, the final dose chosen in part 1 will then be given to all patients who take part. Disease response at 8 weeks will be measured to determine activity of BCT-100 against the four disease types.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of paediatric patients as well as patients lacking capacity to consent to research. The parent(s) or guardian(s) as well as the children were provided with sufficient information to allow patients/parents/legal guardians/legal representatives to make an informed decision about participation as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), patient information in child-appropriate language (where appropriate) was provided and explained to the child and assent recorded. Repeated invasive procedures were minimised. The number of blood samples as well as the amount of blood drawn were adjusted according to a weight.

Background therapy:

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 28 August 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Netherlands: 4 |
| Country: Number of subjects enrolled | United Kingdom: 41 |
| Country: Number of subjects enrolled | Australia: 4 |
| Worldwide total number of subjects | 49 |
| EEA total number of subjects | 4 |

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) | 20 |
| Adolescents (12-17 years) | 22 |
| Adults (18-64 years) | 7 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The trial opened to recruitment on 28th August 2018 and closed to recruitment on 22nd July 2022. The trial recruited from Australia, the Netherlands and the UK.

Pre-assignment

Screening details:

Aged 1- <25 years old at registration

Histologically confirmed disease in one of: Leukaemia, Neuroblastoma, High Grade Glioma or Sarcoma

Radiological or laboratory evidence of disease progression

Measurable bone marrow disease or at least one evaluable radiological site of disease

Adequate liver function

Negative pregnancy test

Period 1

| | |
|------------------------------|----------------|
| Period 1 title | Phase II |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Leukaemia |

Arm description:

Acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML)

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | PEG-BCT-100 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1600U/kg BCT-100 administered as weekly intravenous infusion over one hour. Administered at 7 day intervals (+/- 1 day).

| | |
|------------------|---------|
| Arm title | Sarcoma |
|------------------|---------|

Arm description: -

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | PEG-BCT-100 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1600U/kg BCT-100 administered as weekly intravenous infusion over one hour. Administered at 7 day intervals (+/- 1 day).

| | |
|------------------|-------------------|
| Arm title | High Grade Glioma |
|------------------|-------------------|

Arm description:

As defined by 2016 WHO CNS classification

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|-----------------------|
| Investigational medicinal product name | PEG-BCT-100 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1600U/kg BCT-100 administered as weekly intravenous infusion over one hour. Administered at 7 day intervals (+/- 1 day).

| | |
|------------------|---------------|
| Arm title | Neuroblastoma |
|------------------|---------------|

Arm description: -

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | PEG-BCT-100 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1600U/kg BCT-100 administered as weekly intravenous infusion over one hour. Administered at 7 day intervals (+/- 1 day).

| Number of subjects in period 1 | Leukaemia | Sarcoma | High Grade Glioma |
|---------------------------------------|-----------|---------|-------------------|
| Started | 7 | 13 | 15 |
| Completed | 7 | 13 | 13 |
| Not completed | 0 | 0 | 2 |
| Consent withdrawn by subject | - | - | 1 |
| Progression | - | - | 1 |

| Number of subjects in period 1 | Neuroblastoma |
|---------------------------------------|---------------|
| Started | 14 |
| Completed | 12 |
| Not completed | 2 |
| Consent withdrawn by subject | 1 |
| Progression | 1 |

Period 2

| | |
|------------------------------|----------------|
| Period 2 title | Phase I |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|--|-----------------------|
| Arm title | Leukaemia |
| Arm description: Acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) | |
| Arm type | Experimental |
| Investigational medicinal product name | PEG-BCT-100 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 1600U/kg BCT-100 administered as weekly intravenous infusion over one hour. Administered at 7 day intervals (+/- 1 day). | |
| Arm title | Sarcoma |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | PEG-BCT-100 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 1600U/kg BCT-100 administered as weekly intravenous infusion over one hour. Administered at 7 day intervals (+/- 1 day). | |
| Arm title | High Grade Glioma |
| Arm description: As defined by 2016 WHO CNS classification | |
| Arm type | Experimental |
| Investigational medicinal product name | PEG-BCT-100 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 1600U/kg BCT-100 administered as weekly intravenous infusion over one hour. Administered at 7 day intervals (+/- 1 day). | |

| Number of subjects in period 2^[1] | Leukaemia | Sarcoma | High Grade Glioma |
|---|-----------|---------|-------------------|
| Started | 1 | 1 | 3 |
| Completed | 0 | 1 | 2 |
| Not completed | 1 | 0 | 1 |
| Progression | 1 | - | 1 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Period 1 was defined as Phase II and Period 2 was defined as Phase I as it was expected that Period 1 would be the period for which baseline characteristics were reported.

It was also impossible to put Period 1 as Phase I due to lower numbers in Phase I than Phase II, the system would not allow the number of subjects in Period 2 to exceed the number in Period 1.

Baseline characteristics

Reporting groups

| | |
|---|-------------------|
| Reporting group title | Leukaemia |
| Reporting group description: Acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) | |
| Reporting group title | Sarcoma |
| Reporting group description: - | |
| Reporting group title | High Grade Glioma |
| Reporting group description: As defined by 2016 WHO CNS classification | |
| Reporting group title | Neuroblastoma |
| Reporting group description: - | |

| Reporting group values | Leukaemia | Sarcoma | High Grade Glioma |
|---|---------------|--------------|-------------------|
| Number of subjects | 7 | 13 | 15 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: years | | | |
| median | 7.9 | 12.2 | 12 |
| full range (min-max) | 1.2 to 17.4 | 1.3 to 15.4 | 4.8 to 20 |
| Gender categorical Units: Subjects | | | |
| Female | 3 | 5 | 8 |
| Male | 4 | 8 | 7 |
| Weight Units: kilogram(s) | | | |
| median | 26.9 | 31.5 | 33.3 |
| full range (min-max) | 9.9 to 70.5 | 10.7 to 58.0 | 19.4 to 94.4 |
| Bilirubin Units: umol/L | | | |
| median | 6.0 | 7.0 | 6.0 |
| full range (min-max) | 3.0 to 17.0 | 4.0 to 12.0 | 3.0 to 10.0 |
| ALT Units: U/L | | | |
| median | 40.0 | 14.0 | 17.0 |
| full range (min-max) | 12.0 to 110.0 | 9.0 to 25.0 | 7.0 to 64.0 |

| | | | |
|--|--------|---------|--------|
| Latest Relapse | | | |
| Latest relapse: time from latest relapse to registration in days | | | |
| Units: Days | | | |
| arithmetic mean | 15.4 | 71.8 | 12.3 |
| standard deviation | ± 10.4 | ± 145.9 | ± 4.6 |
| Number of relapses | | | |
| Units: Number | | | |
| arithmetic mean | 2.4 | 3.1 | 1.8 |
| standard deviation | ± 0.9 | ± 2.3 | ± 0.5 |
| Progression | | | |
| Progression: time from progression to registration in days | | | |
| Units: Days | | | |
| arithmetic mean | 2.5 | 130.7 | 47.4 |
| standard deviation | ± 3.5 | ± 127.3 | ± 87.4 |

| Reporting group values | Neuroblastoma | Total | |
|--|---------------|-------|--|
| Number of subjects | 14 | 49 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | | 0 | |
| Newborns (0-27 days) | | 0 | |
| Infants and toddlers (28 days-23 months) | | 0 | |
| Children (2-11 years) | | 0 | |
| Adolescents (12-17 years) | | 0 | |
| Adults (18-64 years) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous | | | |
| Units: years | | | |
| median | 10.3 | | |
| full range (min-max) | 2.0 to 18.8 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 7 | 23 | |
| Male | 7 | 26 | |
| Weight | | | |
| Units: kilogram(s) | | | |
| median | 25.7 | | |
| full range (min-max) | 12.0 to 86.1 | - | |
| Bilirubin | | | |
| Units: umol/L | | | |
| median | 5.0 | | |
| full range (min-max) | 3.0 to 11.0 | - | |
| ALT | | | |
| Units: U/L | | | |
| median | 24.0 | | |
| full range (min-max) | 13.0 to 115.0 | - | |
| Latest Relapse | | | |
| Latest relapse: time from latest relapse to registration in days | | | |

| | | | |
|--|---------|---|--|
| Units: Days | | | |
| arithmetic mean | 65.7 | | |
| standard deviation | ± 106.1 | - | |
| Number of relapses | | | |
| Units: Number | | | |
| arithmetic mean | 3.0 | | |
| standard deviation | ± 1.4 | - | |
| Progression | | | |
| Progression: time from progression to registration in days | | | |
| Units: Days | | | |
| arithmetic mean | 65.3 | | |
| standard deviation | ± 70.6 | - | |

End points

End points reporting groups

| | |
|---|-------------------|
| Reporting group title | Leukaemia |
| Reporting group description: Acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) | |
| Reporting group title | Sarcoma |
| Reporting group description: - | |
| Reporting group title | High Grade Glioma |
| Reporting group description: As defined by 2016 WHO CNS classification | |
| Reporting group title | Neuroblastoma |
| Reporting group description: - | |
| Reporting group title | Leukaemia |
| Reporting group description: Acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) | |
| Reporting group title | Sarcoma |
| Reporting group description: - | |
| Reporting group title | High Grade Glioma |
| Reporting group description: As defined by 2016 WHO CNS classification | |

Primary: Phase I Primary Endpoint - DLTs

| | |
|--|--|
| End point title | Phase I Primary Endpoint - DLTs ^[1] |
| End point description: | |
| End point type | Primary |
| End point timeframe: 3 evaluable patients were recruited to Phase I Cohort I of the PARC trial and received trial treatment (BCT-100) and monitored for 28 days following treatment for the occurrence of any dose-limiting toxicities (DLTs). | |
| 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: Occurrence of DLTs were assessed by Statistician and presented to DMC members to confirm if any DLTs had occurred. No statistical analysis took place for this endpoint. | |

| End point values | Leukaemia | Sarcoma | High Grade Glioma | |
|-----------------------------|------------------|-----------------|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[2] | 1 | 2 | |
| Units: Number of DLTs | | 0 | 0 | |

Notes:

[2] - Patient progressed and did not reach end point

Statistical analyses

No statistical analyses for this end point

Primary: Phase I Primary Endpoint - Successful Arginine Depletion

| | |
|-----------------|---|
| End point title | Phase I Primary Endpoint - Successful Arginine Depletion ^[3] |
|-----------------|---|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

3 evaluable patients were recruited to Phase I Cohort I of the trial. Optimal dose was measured by the complete depletion of arginine. This is defined as adequated arginine depletion (AAD) <8µM arginine in the blood after 4 doses of BCT-100.

Notes:

[3] - 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: This primary endpoint was based on successful depletion of arginine in patients (<=8µM in blood). No formal statistical analysis took place.

| End point values | Leukaemia | Sarcoma | High Grade Glioma | |
|-----------------------------|------------------|-----------------|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[4] | 1 | 2 | |
| Units: µM | | | | |
| number (not applicable) | | 5.25 | 4.75 | |

Notes:

[4] - Patient progressed and did not reach endpoint

Statistical analyses

No statistical analyses for this end point

Primary: Phase II - Disease Response after 8 Weeks of treatment with BCT-100

| | |
|-----------------|--|
| End point title | Phase II - Disease Response after 8 Weeks of treatment with BCT-100 ^[5] |
|-----------------|--|

End point description:

Response assessment will be conducted as a Modified Intention-To-Treat (MITT) analysis, any patient who withdraws or dies prior to starting treatment will not be considered evaluable and will be replaced. A true response rate greater than 20% is of interest in any of the four disease groups. The trial will recruit 13 patients per group for the phase II component. Patients who were treated at the selected Phase II dose in the Phase I component will contribute to this 13 patient requirement. Response definitions

are different for each disease group and are based on specific criteria related that disease e.g. Leukaemia, Solid tumours.

Each group will have the response rate individually assessed using Bayesian posterior probability plots and 95% Credible Intervals. Posterior Probabilities will be calculated for the true response rate in each arm using a non-informative prior Beta(0.5, 0.5)

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Response for primary outcome is assessed at 8 weeks or potentially earlier in the case of progressive disease.

Notes:

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

Justification: Statistical analysis (Bayesian) is described in description of end point and plots are attached - could not add in the statistical analysis section as it would not allow a single arm analysis to be added and each disease group was assessed separately, no comparisons were made between arms.

| End point values | Leukaemia | Sarcoma | High Grade Glioma | Neuroblastoma |
|-----------------------------|-----------------|-----------------|-------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 7 | 13 | 13 | 12 |
| Units: Number of responses | 0 | 0 | 0 | 0 |

| | |
|-----------------------------------|---|
| Attachments (see zip file) | Leukaemia: Posterior Probability Plot/Posterior_Leuk.jpg Neuroblastoma: Posterior Probability Plot/Posterior_Neuro.jpg High Grade Glioma: Posterior Probability Plot/Posterior_HGG. Sarcoma: Posterior Probability Plot/Posterior_Sarc.jpg |
|-----------------------------------|---|

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival

| | |
|--|---------------------------|
| End point title | Progression-Free Survival |
| End point description: Measured from the date of registration, an event here is defined as either progression or death, patients are followed up until they have either experienced an event or are censored at date last seen. Kaplan-Meier plots will be produced, estimates of median PFS and PFS at 6 and 12 months will be reported along with associated confidence intervals (where they can be calculated). | |
| End point type | Secondary |
| End point timeframe: Measured from the date of registration, an event here is defined as either progression or death, patients are followed up until they have either experienced an event or are censored at date last seen. | |

| End point values | Leukaemia | Sarcoma | High Grade Glioma | Neuroblastoma |
|----------------------------------|------------------|------------------|-------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 7 | 13 | 13 | 12 |
| Units: Months | | | | |
| median (confidence interval 95%) | 1.1 (0.5 to 1.7) | 1.8 (0.9 to 1.9) | 1.5 (0.7 to 2.0) | 1.8 (0.6 to 2.1) |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | Progression-Free Survival: Kaplan-Meier Plot/PFS_grp.pdf |
|-----------------------------------|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

| | |
|--|------------------|
| End point title | Overall Survival |
| End point description: Kaplan-Meier plots will be produced, estimates of median survival and survival at 6 and 12 months will | |

be reported along
with associated confidence intervals (where they can be calculated).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Measured from the date of registration, an event here is defined as death, patients are followed up until they have either died or are censored at date last seen.

| End point values | Leukaemia | Sarcoma | High Grade Glioma | Neuroblastoma |
|-----------------------------|-----------------|-----------------|-------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 7 | 13 | 13 | 12 |
| Units: Months | | | | |
| median (standard error) | 1.28 (± 0.043) | 3.5 (± 0.985) | 2.2 (± 0.315) | 2.9 (± 5.042) |

| | |
|----------------------------|--|
| Attachments (see zip file) | Overall Survival: Kaplan-Meier Plot/OS_grp.pdf |
|----------------------------|--|

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Disease response (CR / PR) at any time during treatment with BCT-100

| | |
|-----------------|---|
| End point title | Disease response (CR / PR) at any time during treatment with BCT-100 |
|-----------------|---|

End point description:

The outcome will be tabulated as best disease response by response categories Complete Response/Partial Response/Stable Disease/Progressive Disease (CR/PR/SD/PD) for each patient in each disease group, at any time during treatment with BCT-100, with CR/PR equal to disease response.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

For this exploratory end point, the best response at any time while on treatment is reported for each patient.

| End point values | Leukaemia | Sarcoma | High Grade Glioma | Neuroblastoma |
|-----------------------------|-----------------|-----------------|-------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 7 | 13 | 13 | 12 |
| Units: Number of responses | | | | |
| CR | 0 | 0 | 0 | 0 |
| PR | 0 | 0 | 1 | 0 |
| SD | 1 | 3 | 1 | 3 |
| PD | 1 | 4 | 3 | 4 |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Details of all AEs will be documented and reported from the date of informed consent until 28 days after the administration of the last dose of trial treatment.

Adverse event reporting additional description:

AEs will be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

| | |
|--------------------|-----|
| Dictionary version | 4.0 |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Leukaemia |
|-----------------------|-----------|

Reporting group description:

Acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML)

| | |
|-----------------------|---------------|
| Reporting group title | Neuroblastoma |
|-----------------------|---------------|

Reporting group description: -

| | |
|-----------------------|---------|
| Reporting group title | Sarcoma |
|-----------------------|---------|

Reporting group description: -

| | |
|-----------------------|-------------------|
| Reporting group title | High Grade Glioma |
|-----------------------|-------------------|

Reporting group description:

As defined by 2016 WHO CNS classification

| Serious adverse events | Leukaemia | Neuroblastoma | Sarcoma |
|---|----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 7 (85.71%) | 6 / 12 (50.00%) | 7 / 13 (53.85%) |
| number of deaths (all causes) | 7 | 10 | 13 |
| number of deaths resulting from adverse events | 1 | 0 | 0 |
| Cardiac disorders | | | |
| Atrial Ectopics | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (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 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (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 |
| Nervous system disorders | | | |
| Headache | | | |

| | | | |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (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 | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Fever | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 3 / 12 (25.00%) | 5 / 13 (38.46%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| infusion related infection | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (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 |
| Immune system disorders | | | |
| Allergic reaction | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (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 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (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 | | | |
| distress due to fluid overload | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (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 |
| dyspnea | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 2 / 13 (15.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory arrest | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Polyuria Polydispsia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (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 | | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (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 |
| Neck pain | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (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 |
| upper respiratory infection | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacteriémie | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (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 |

| | | | |
|---|-------------------|--|--|
| Serious adverse events | High Grade Glioma | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 13 (53.85%) | | |
| number of deaths (all causes) | 12 | | |
| number of deaths resulting from adverse events | 0 | | |
| Cardiac disorders | | | |
| Atrial Ectopics | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|-----------------|--|--|
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Fever | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| infusion related infection | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Allergic reaction | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| distress due to fluid overload | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| dyspnea | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory arrest | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Polyuria Polydispsia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neck pain | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| upper respiratory infection | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bacterienie | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Leukaemia | Neuroblastoma | Sarcoma |
|---|-----------------|-------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 7 / 7 (100.00%) | 12 / 12 (100.00%) | 13 / 13 (100.00%) |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thromboembolic event | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypertension | | | |

| | | | |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 1 | 0 | 1 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 2 / 12 (16.67%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| General disorders and administration site conditions | | | |
| fever | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 5 / 12 (41.67%) | 6 / 13 (46.15%) |
| occurrences (all) | 2 | 15 | 9 |
| Pain | | | |
| subjects affected / exposed | 4 / 7 (57.14%) | 4 / 12 (33.33%) | 7 / 13 (53.85%) |
| occurrences (all) | 4 | 7 | 10 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 3 / 12 (25.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 5 | 1 |
| Runny nose | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 2 / 13 (15.38%) |
| occurrences (all) | 0 | 0 | 4 |
| Weakness | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypothermia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Common cold | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Chills | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Coryzal symptoms | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Night sweats | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 13 (7.69%) 1 |
| Excess transpiration subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 13 (0.00%) 0 |
| Localised oedema subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 13 (7.69%) 1 |
| Oedema trunk subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Immune system disorders Allergic reaction subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 1 / 12 (8.33%) 1 | 0 / 13 (0.00%) 0 |
| Reproductive system and breast disorders Vaginal pain subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Apnea subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 1 / 12 (8.33%) 1 | 0 / 13 (0.00%) 0 |
| Pulmonary oedema subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Respiratory distress subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Respiratory failure subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 13 (0.00%) 0 |
| Runny nose | | | |

| | | | |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Cough | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 2 / 12 (16.67%) | 3 / 13 (23.08%) |
| occurrences (all) | 0 | 2 | 5 |
| Dyspnea | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 12 (8.33%) | 4 / 13 (30.77%) |
| occurrences (all) | 1 | 1 | 6 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 1 | 1 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 2 / 13 (15.38%) |
| occurrences (all) | 0 | 0 | 3 |
| Sore throat | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 2 / 13 (15.38%) |
| occurrences (all) | 0 | 0 | 2 |
| Psychiatric disorders | | | |
| Confusion | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 1 | 0 | 1 |
| Euphoria | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Libido decreased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Low mood | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Restlessness | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Anxiety | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 3 / 13 (23.08%) |
| occurrences (all) | 0 | 0 | 4 |

| | | | |
|--------------------------------------|----------------|-----------------|-----------------|
| Insomnia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Investigations | | | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 5 / 7 (71.43%) | 5 / 12 (41.67%) | 6 / 13 (46.15%) |
| occurrences (all) | 13 | 12 | 11 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 4 / 7 (57.14%) | 7 / 12 (58.33%) | 2 / 13 (15.38%) |
| occurrences (all) | 8 | 11 | 2 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 3 / 7 (42.86%) | 6 / 12 (50.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 5 | 14 | 0 |
| Creatinine decreased | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 2 / 12 (16.67%) | 2 / 13 (15.38%) |
| occurrences (all) | 2 | 6 | 7 |
| Chloride high | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bicarbonate low | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Creatinine increased | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 0 / 12 (0.00%) | 2 / 13 (15.38%) |
| occurrences (all) | 6 | 0 | 2 |
| GGT increased | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Monocyte count increased | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 2 / 13 (15.38%) |
| occurrences (all) | 1 | 0 | 3 |
| MCV decrease | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 2 / 13 (15.38%) |
| occurrences (all) | 0 | 0 | 2 |
| MCV increase | | | |

| | | | |
|----------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 3 / 13 (23.08%) |
| occurrences (all) | 2 | 0 | 4 |
| CRP increased | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Eosinophils decreased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 12 (8.33%) | 2 / 13 (15.38%) |
| occurrences (all) | 1 | 1 | 2 |
| Lymphocyte count increased | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Phosphate high | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 2 | 0 | 1 |
| ALT decreased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Creatinine decrease | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 3 |
| Weight loss | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 2 / 13 (15.38%) |
| occurrences (all) | 0 | 1 | 2 |
| Elevated Bicarbonate Levels | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mean Corpuscular Volume Decrease | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Monocytes low | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Haemoglobin increased | | | |

| | | | |
|---------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| MCHC High | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 2 |
| alkaline phosphatase decrease | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| cholesterol high | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| INR increased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Basophils high | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urine output decreased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lactate dehydrogenase increase | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haemoglobin low | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Weight gain | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Mean cell haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Activated partial thromboplastin time | | | |

| | | | |
|--|----------------|----------------|----------------|
| prolonged | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mean cell haemoglobin increased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Chloride increased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| High ferritine | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thrombin time increased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Increased urine output | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood prolactin abnormal | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Bruising | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 2 | 0 | 1 |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 4 | 0 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 12 (8.33%) | 1 / 13 (7.69%) |
| occurrences (all) | 1 | 1 | 1 |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nervous system disorders | | | |

| | | | |
|---------------------------------|----------------|-----------------|-----------------|
| Headache | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 5 / 13 (38.46%) |
| occurrences (all) | 0 | 0 | 8 |
| Lethargy | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 2 / 12 (16.67%) | 2 / 13 (15.38%) |
| occurrences (all) | 1 | 3 | 3 |
| Dysarthria | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ataxia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Facial muscle weakness | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Paresthesia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Hemiplegia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Spasticity | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sleep disturbance - wakes early | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Paraplegia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|--------------------|---------------------|---------------------|
| Bladder emptying disorder subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Memory impairment subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Dysaesthesia subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 13 (7.69%) 1 |
| Tremor subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Imbalance subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 13 (0.00%) 0 |
| Somnolence subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Spinal cord injury subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Polydipsia subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Dysphagia subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Hypersomnia subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Bowel emptying disorder subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Dysgeusia subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |

| | | | |
|---|-----------------------|-----------------------|-----------------------|
| Intratumoural haemorrhage and surrounding cerebral oedema subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 13 (7.69%) 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 7 / 7 (100.00%) 24 | 9 / 12 (75.00%) 18 | 8 / 13 (61.54%) 14 |
| Platelet count decreased subjects affected / exposed occurrences (all) | 6 / 7 (85.71%) 49 | 7 / 12 (58.33%) 9 | 0 / 13 (0.00%) 0 |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 5 / 7 (71.43%) 15 | 5 / 12 (41.67%) 7 | 3 / 13 (23.08%) 5 |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 6 / 7 (85.71%) 18 | 5 / 12 (41.67%) 9 | 1 / 13 (7.69%) 1 |
| Haematocrit decreased subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 2 / 12 (16.67%) 2 | 5 / 13 (38.46%) 11 |
| Neutrophil count increased subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 3 / 13 (23.08%) 10 |
| Red blood cell count decreased subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 1 / 12 (8.33%) 1 | 3 / 13 (23.08%) 7 |
| Platelet count increased subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 12 (8.33%) 1 | 3 / 13 (23.08%) 5 |
| White blood cell count increased subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 2 / 13 (15.38%) 5 |
| Febrile neutropenia | | | |

| | | | |
|--------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 2 / 7 (28.57%) | 2 / 12 (16.67%) | 1 / 13 (7.69%) |
| occurrences (all) | 2 | 2 | 1 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 1 | 0 | 1 |
| Red blood cell count increased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 2 |
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Enlarged lymph node | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haematocrit increased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Buzzing in left ear | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorders | | | |
| Optic nerve disorder | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| blurred vision | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Papilledema | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |

| | | | |
|-----------------------------|----------------|-----------------|-----------------|
| Vomiting | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 3 / 12 (25.00%) | 6 / 13 (46.15%) |
| occurrences (all) | 2 | 10 | 12 |
| Constipation | | | |
| subjects affected / exposed | 3 / 7 (42.86%) | 3 / 12 (25.00%) | 4 / 13 (30.77%) |
| occurrences (all) | 4 | 3 | 4 |
| Nausea | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 12 (8.33%) | 6 / 13 (46.15%) |
| occurrences (all) | 1 | 5 | 8 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 12 (8.33%) | 2 / 13 (15.38%) |
| occurrences (all) | 1 | 1 | 4 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 2 / 12 (16.67%) | 2 / 13 (15.38%) |
| occurrences (all) | 0 | 3 | 2 |
| stomach pain | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 2 / 13 (15.38%) |
| occurrences (all) | 0 | 1 | 2 |
| Oral pain | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 2 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| blood in stool | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dental caries | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|--|---------------------|---------------------|---------------------|
| bloating subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Enterocolitis subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Soft stool subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 13 (0.00%) 0 |
| Crohn's disease subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| hypersalivation subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Gait disturbance subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Non-cardiac chest pain subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 13 (7.69%) 1 |
| Skin and subcutaneous tissue disorders Blister on abdomen subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 13 (0.00%) 0 |
| Dry skin subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Itching subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 13 (7.69%) 1 |
| Photosensitivity subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Pruritus | | | |

| | | | |
|--------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rash-Graft Versus Host Disease | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Shingles | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin atrophy | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin ulceration | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Alopecia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 2 / 12 (16.67%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 1 / 12 (8.33%) | 1 / 13 (7.69%) |
| occurrences (all) | 2 | 1 | 1 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Bladder perforation | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bladder spasm | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cystitis noninfective | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|-----------------------------|----------------|-----------------|----------------|
| Polyuria | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urea high | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urate low | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Urea decreased | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 4 / 12 (33.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 2 | 9 | 0 |
| Urea increased | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 2 / 12 (16.67%) | 1 / 13 (7.69%) |
| occurrences (all) | 2 | 4 | 3 |
| Endocrine disorders | | | |
| Cushingoid | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| TSH level decreased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| FSH level decreased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| LH level decreased | | | |

| | | | |
|---|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoparathyroidism | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Flank pain | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Joint range of motion decreased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Muscle weakness lower limb | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Muscle weakness right-sided | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle weakness trunk | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pain in right shoulder | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Back pain | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Generalised muscle weakness | | | |

| | | | |
|-------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Muscle weakness left-sided | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 2 / 12 (16.67%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 2 | 2 |
| Infections and infestations | | | |
| Bacillus Cereus | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| staphylococcus epidermis | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Common cold? No virology done | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Common cold? Virus unknown | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hand-foot-and-mouth disease | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Herpetic lip lesions | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|------------------------------------|----------------|----------------|----------------|
| Nail infection | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oral fungal infection | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinovirus infection | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Unknown viral cough | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory infection | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 12 (8.33%) | 1 / 13 (7.69%) |
| occurrences (all) | 1 | 1 | 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 4 |
| Metabolism and nutrition disorders | | | |
| Chloride levels decreased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| hyperglycemia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| hyperkalemia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypertriglyceridaemia | | | |

| | | | |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 1 | 0 | 1 |
| Increased thirst | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| weight gain | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anorexia nervosa | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 12 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypernatraemia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 3 / 12 (25.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 1 | 3 | 1 |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 12 (8.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 4 / 7 (57.14%) | 3 / 12 (25.00%) | 2 / 13 (15.38%) |
| occurrences (all) | 9 | 5 | 2 |
| Hypokalaemia | | | |
| subjects affected / exposed | 5 / 7 (71.43%) | 0 / 12 (0.00%) | 4 / 13 (30.77%) |
| occurrences (all) | 14 | 0 | 12 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 3 / 7 (42.86%) | 2 / 12 (16.67%) | 0 / 13 (0.00%) |
| occurrences (all) | 6 | 5 | 0 |
| Hyponatraemia | | | |

| | | | |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 7 (28.57%) | 3 / 12 (25.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 3 | 5 | 1 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 1 / 12 (8.33%) | 2 / 13 (15.38%) |
| occurrences (all) | 4 | 2 | 2 |

| Non-serious adverse events | High Grade Glioma | | |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 13 (100.00%) | | |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Thromboembolic event | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Hypertension | | | |
| subjects affected / exposed | 3 / 13 (23.08%) | | |
| occurrences (all) | 4 | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| General disorders and administration site conditions | | | |
| fever | | | |
| subjects affected / exposed | 3 / 13 (23.08%) | | |
| occurrences (all) | 7 | | |
| Pain | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 2 | | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 3 | | |
| Runny nose | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Weakness | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypothermia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Common cold | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Chills | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Coryzal symptoms | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Night sweats | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Excess transpiration | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Localised oedema | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oedema trunk | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Immune system disorders | | | |
| Allergic reaction | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Reproductive system and breast disorders | | | |
| Vaginal pain | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| Apnea | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Runny nose | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cough | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Dyspnea | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 4 | | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sore throat | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Psychiatric disorders | | | |
| Confusion | | | |

| | | | |
|--------------------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Euphoria | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Libido decreased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Low mood | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Restlessness | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| Investigations | | | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 10 / 13 (76.92%) | | |
| occurrences (all) | 17 | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 13 (23.08%) | | |
| occurrences (all) | 5 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 2 | | |
| Creatinine decreased | | | |
| subjects affected / exposed | 3 / 13 (23.08%) | | |
| occurrences (all) | 4 | | |
| Chloride high | | | |

| | | | |
|--------------------------------|-----------------|--|--|
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 13 | | |
| Bicarbonate low | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 5 | | |
| Creatinine increased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| GGT increased | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 2 | | |
| Monocyte count increased | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 3 | | |
| MCV decrease | | | |
| subjects affected / exposed | 3 / 13 (23.08%) | | |
| occurrences (all) | 4 | | |
| MCV increase | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| CRP increased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eosinophils decreased | | | |
| subjects affected / exposed | 3 / 13 (23.08%) | | |
| occurrences (all) | 4 | | |
| Alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lymphocyte count increased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Phosphate high | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| ALT decreased | | | |

| | | | |
|----------------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| Creatinine decrease | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Weight loss | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Elevated Bicarbonate Levels | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| Mean Corpuscular Volume Decrease | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| Monocytes low | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Haemoglobin increased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| MCHC High | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| alkaline phosphatase decrease | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| cholesterol high | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| INR increased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Basophils high | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Urine output decreased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lactate dehydrogenase increase | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Haemoglobin low | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Weight gain | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Mean cell haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Activated partial thromboplastin time prolonged | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Mean cell haemoglobin increased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Chloride increased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| High ferritine | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Thrombin time increased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Increased urine output | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|--|---|--|--|
| Blood prolactin abnormal subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Injury, poisoning and procedural complications Bruising subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | | |
| Cardiac disorders Tachycardia subjects affected / exposed occurrences (all) Sinus tachycardia subjects affected / exposed occurrences (all) Cardiac arrest subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 2 / 13 (15.38%) 2 0 / 13 (0.00%) 0 | | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) Lethargy subjects affected / exposed occurrences (all) Dysarthria subjects affected / exposed occurrences (all) Seizure subjects affected / exposed occurrences (all) Hydrocephalus subjects affected / exposed occurrences (all) Ataxia subjects affected / exposed occurrences (all) | 5 / 13 (38.46%) 9 4 / 13 (30.77%) 4 2 / 13 (15.38%) 4 4 / 13 (30.77%) 5 3 / 13 (23.08%) 3 0 / 13 (0.00%) 0 | | |

| | | | |
|---------------------------------|-----------------|--|--|
| Facial muscle weakness | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 2 | | |
| Paresthesia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Hemiplegia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Spasticity | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Sleep disturbance - wakes early | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Paraplegia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Bladder emptying disorder | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Memory impairment | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Dysaesthesia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tremor | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Imbalance | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |

| | | | |
|---|-----------------|--|--|
| Spinal cord injury | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Polydipsia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Hypersomnia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Bowel emptying disorder | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Intratumoural haemorrhage and surrounding cerebral oedema | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 7 / 13 (53.85%) | | |
| occurrences (all) | 20 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 2 | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 6 / 13 (46.15%) | | |
| occurrences (all) | 29 | | |
| Neutrophil count decreased | | | |

| | | | |
|----------------------------------|-----------------|--|--|
| subjects affected / exposed | 4 / 13 (30.77%) | | |
| occurrences (all) | 10 | | |
| Haematocrit decreased | | | |
| subjects affected / exposed | 6 / 13 (46.15%) | | |
| occurrences (all) | 8 | | |
| Neutrophil count increased | | | |
| subjects affected / exposed | 5 / 13 (38.46%) | | |
| occurrences (all) | 7 | | |
| Red blood cell count decreased | | | |
| subjects affected / exposed | 4 / 13 (30.77%) | | |
| occurrences (all) | 7 | | |
| Platelet count increased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| White blood cell count increased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypertension | | | |
| subjects affected / exposed | 3 / 13 (23.08%) | | |
| occurrences (all) | 4 | | |
| Red blood cell count increased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Enlarged lymph node | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Haematocrit increased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Ear and labyrinth disorders | | | |

| | | | |
|--|----------------------|--|--|
| Ear pain subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | | |
| Buzzing in left ear subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Eye disorders Optic nerve disorder subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| blurred vision subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | | |
| Papilledema subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) | 5 / 13 (38.46%) 9 | | |
| Constipation subjects affected / exposed occurrences (all) | 4 / 13 (30.77%) 8 | | |
| Nausea subjects affected / exposed occurrences (all) | 3 / 13 (23.08%) 3 | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 2 / 13 (15.38%) 2 | | |
| Dysphagia subjects affected / exposed occurrences (all) | 3 / 13 (23.08%) 6 | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | | |
| stomach pain | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oral pain | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| blood in stool | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dental caries | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| bloating | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Soft stool | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Crohn's disease | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| hypersalivation | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Gait disturbance | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 2 | | |
| Non-cardiac chest pain | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Blister on abdomen | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dry skin | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Itching | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Photosensitivity | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pruritus | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Rash-Graft Versus Host Disease | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Shingles | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin atrophy | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Skin ulceration | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Alopecia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|---|----------------------|--|--|
| Rash maculo-papular subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | | |
| Bladder perforation subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Bladder spasm subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | | |
| Cystitis noninfective subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | | |
| Polyuria subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Urea high subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Urinary incontinence subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Urinary retention subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Urate low subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | | |
| Urea decreased subjects affected / exposed occurrences (all) | 2 / 13 (15.38%) 2 | | |
| Urea increased | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 3 / 13 (23.08%) | | |
| occurrences (all) | 6 | | |
| Endocrine disorders | | | |
| Cushingoid | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| TSH level decreased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| FSH level decreased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| LH level decreased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Hypoparathyroidism | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Flank pain | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Joint range of motion decreased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Muscle weakness lower limb | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Muscle weakness right-sided | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Muscle weakness trunk | | | |

| | | | |
|-------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Pain in right shoulder | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 2 | | |
| Generalised muscle weakness | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Muscle weakness left-sided | | | |
| subjects affected / exposed | 5 / 13 (38.46%) | | |
| occurrences (all) | 5 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Bacillus Cereus | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| staphylococcus epidermis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Common cold? No virology done | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |

| | | | |
|---|---------------------|--|--|
| Common cold? Virus unknown subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Conjunctivitis subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | | |
| COVID-19 subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Hand-foot-and-mouth disease subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Herpetic lip lesions subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | | |
| Nail infection subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | | |
| Oral fungal infection subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 2 | | |
| Rhinovirus infection subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Sepsis subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | | |
| Unknown viral cough subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Upper respiratory infection subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | | |

| | | | |
|------------------------------------|----------------|--|--|
| Metabolism and nutrition disorders | | | |
| Chloride levels decreased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| hyperglycemia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| hyperkalemia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Increased thirst | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| weight gain | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Anorexia nervosa | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| Blood glucose increased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| Hypernatraemia | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 2 | | |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | | |
| occurrences (all) | 4 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 3 / 13 (23.08%) | | |
| occurrences (all) | 3 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 2 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------|--|
| 29 May 2020 | Update of Senior Trial Coordinator and Trial Coordinator, NCC for France updated, Added email address for DLT & SAE forms, Removed the word international from title in Trial Synopsis, Clarification of timepoints at which to collect PD's/PK's, Section 12.1.2 spelling error corrected (Events), To add that monitoring for Dose Limiting Toxicities will also be completed for the first 28 days of treatment in Phase II, Updated pregnancy frequency for Republic of Ireland, Updated age inclusion criteria for patients in the Republic of Ireland, Removal of the following statement "Comparatively arginase appeared more effective than asparaginase – the only current metabolic enzyme therapy in upfront clinical protocols for leukaemia", Added the following in section 16.1; " Any patient who withdraws or dies prior to starting treatment will not be considered evaluable and will be replaced.", Exclusion criteria added: History of an anaphylactic reaction to kanamycin, Updated section 12.2.4.5: Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to Principal Investigator within 3 days. A copy should be filed in the ISF, Added to section 17.4: The Sponsor will ensure that any potential signal for lack of efficacy that the TMG are aware of in the PARC study is brought to the attention of the DMC and is appropriately investigated. Subsequently, the DMC can make recommendations to the TMG/sponsor regarding any concerns for lack of efficacy, Addition of note to the following sections: Trial Schema, section 3.2 and section 7.2.1 (Note: Phase I reported in Jan 2019 with 1600U/kg BCT-100 defined as the recommended Phase II dose. Phase II opened to recruitment on 16th January 2019), Added section: 7.5.7 GCSF to table of contents. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported