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
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: Occurence of DLTs were assessed by Statistician and presented to DMC members to confirm if any DLTs had occured. 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 depltion (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 (<=8muM 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
Bacterienie			
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	0 / 7 (0.00%)	0 / 12 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Excess transpiration			
subjects affected / exposed	0 / 7 (0.00%)	1 / 12 (8.33%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Localised oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Oedema trunk			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Allergic reaction			
subjects affected / exposed	1 / 7 (14.29%)	1 / 12 (8.33%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Reproductive system and breast disorders			
Vaginal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Apnea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 12 (8.33%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Pulmonary oedema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Respiratory distress			
subjects affected / exposed	1 / 7 (14.29%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Respiratory failure			
subjects affected / exposed	0 / 7 (0.00%)	1 / 12 (8.33%)	0 / 13 (0.00%)
occurrences (all)	0	1	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	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Memory impairment			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Dysaesthesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Imbalance			
subjects affected / exposed	0 / 7 (0.00%)	1 / 12 (8.33%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Spinal cord injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Polydipsia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Dysphagia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Hypersomnia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Bowel emptying disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0

Intratumoural haemorrage and surrounding cerebral oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 7 (100.00%)	9 / 12 (75.00%)	8 / 13 (61.54%)
occurrences (all)	24	18	14
Platelet count decreased			
subjects affected / exposed	6 / 7 (85.71%)	7 / 12 (58.33%)	0 / 13 (0.00%)
occurrences (all)	49	9	0
White blood cell count decreased			
subjects affected / exposed	5 / 7 (71.43%)	5 / 12 (41.67%)	3 / 13 (23.08%)
occurrences (all)	15	7	5
Neutrophil count decreased			
subjects affected / exposed	6 / 7 (85.71%)	5 / 12 (41.67%)	1 / 13 (7.69%)
occurrences (all)	18	9	1
Haematocrit decreased			
subjects affected / exposed	1 / 7 (14.29%)	2 / 12 (16.67%)	5 / 13 (38.46%)
occurrences (all)	1	2	11
Neutrophil count increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	3 / 13 (23.08%)
occurrences (all)	0	0	10
Red blood cell count decreased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 12 (8.33%)	3 / 13 (23.08%)
occurrences (all)	1	1	7
Platelet count increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 12 (8.33%)	3 / 13 (23.08%)
occurrences (all)	0	1	5
White blood cell count increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	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	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Enterocolitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Soft stool			
subjects affected / exposed	0 / 7 (0.00%)	1 / 12 (8.33%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Crohn's disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
hypersalivation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Blister on abdomen			
subjects affected / exposed	0 / 7 (0.00%)	1 / 12 (8.33%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	1 / 7 (14.29%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Itching			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Photosensitivity			
subjects affected / exposed	1 / 7 (14.29%)	0 / 12 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	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	1 / 13 (7.69%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Bruising			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Sinus tachycardia			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Cardiac arrest			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 13 (38.46%)		
occurrences (all)	9		
Lethargy			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	4		
Dysarthria			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	4		
Seizure			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	5		
Hydrocephalus			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Ataxia			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	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 occurrences (all)	1 / 13 (7.69%) 1		
Polydipsia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Dysphagia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Hypersomnia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Bowel emptying disorder subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Dysgeusia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Intratumoural haemorrage and surrounding cerebral oedema subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Dizziness subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	7 / 13 (53.85%) 20		
Platelet count decreased subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2		
White blood cell count decreased subjects affected / exposed occurrences (all)	6 / 13 (46.15%) 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	0 / 13 (0.00%)		
occurrences (all)	0		
Buzzing in left ear			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Eye disorders			
Optic nerve disorder			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
blurred vision			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Papilledema			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	5 / 13 (38.46%)		
occurrences (all)	9		
Constipation			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	8		
Nausea			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Dysphagia			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	6		
Abdominal pain			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	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	1 / 13 (7.69%)		
occurrences (all)	1		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Bladder perforation			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Bladder spasm			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Cystitis noninfective			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Polyuria			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Urea high			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Urinary incontinence			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Urinary retention			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Urate low			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Urea decreased			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	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	1 / 13 (7.69%)			
occurrences (all)	1			
Conjunctivitis				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences (all)	0			
COVID-19				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Hand-foot-and-mouth disease				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Herpetic lip lesions				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences (all)	0			
Nail infection				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences (all)	0			
Oral fungal infection				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	2			
Rhinovirus infection				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Sepsis				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences (all)	0			
Unknown viral cough				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Upper respiratory infection				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Urinary tract infection				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences (all)	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