Clinical trial results:
Phase I, open label, dose-escalation study followed by a safety expansion part to evaluate the safety, expansion and persistence of a single dose of UCART19 (allogeneic engineered T-cells expressing anti-CD19 chimeric antigen receptor), administered intravenously in patients with relapsed or refractory CD19 positive B-cell acute lymphoblastic leukaemia (B-ALL)). CALM study (UCART19 in Advanced Lymphoid Malignancies).

Summary

EudraCT number	2016-000296-24
Trial protocol	FR
Global end of trial date	28 July 2020
Results information	
Result version number	v1 (current)
This version publication date	21 July 2021
First version publication date	21 July 2021

Trial information

Trial identification	
Sponsor protocol code	CL1-68587-002
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02746952
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50 rue Carnot, Suresnes, France, 92284
Public contact	Therapeutic Area in Oncology, Institut de Recherches Internationales Servier, +33 1 55 72 43 66, clinicaltrials@servier.com
Scientific contact	Therapeutic Area in Oncology, Institut de Recherches Internationales Servier, +33 1 55 72 43 66, clinicaltrials@servier.com
Sponsor organisation name	Servier R&D Ltd
Sponsor organisation address	Sefton House, Sefton Park, Bell Hill, Stoke Poges, Slough, Berkshire, United Kingdom, SL2 4JS
Public contact	Therapeutic Area in Oncology, Institut de Recherches Internationales Servier, +33 1 55 72 43 66, clinicaltrials@servier.com
Scientific contact	Therapeutic Area in Oncology, Institut de Recherches Internationales Servier, +33 1 55 72 43 66, clinicaltrials@servier.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 July 2020
Global end of trial reached?	Yes
Global end of trial date	28 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of ascending doses of UCART19, to determine the maximum tolerated dose (MTD), the recommended dose (RD) and the lymphodepletion (LD) regimen (dose escalation part).
To assess the safety and tolerability of the RD for UCART19 during the safety dose expansion part.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 August 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	15 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 2
Country: Number of subjects enrolled	United States: 6
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	United Kingdom: 11
Worldwide total number of subjects	25
EEA total number of subjects	6

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	25
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients were male or female participants aged ≥ 16 years, up to < 70 years old, with R/R CD19+ B-ALL, as per NCCN guidelines, 2019 (National Comprehensive Cancer Network, 2019).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	1E5 cells/kg

Arm description:

At D-7 , a LymphoDepletion (LD) was initiated. The LD treatment was the enhancement of homeostatic proliferation of the infused UCART19 cells by deep and prolonged depletion of host immune cells. It combined fludarabine 30 mg/m2/day IV, cyclophosphamide 500 mg/m2/day IV and alemtuzumab IV 0.2 mg/kg/day or 8 mg/day or 12 mg/day.
The treatment period started at time of UCART19 administration at D0 up to D84. UCART19 is a frozen suspension of allogeneic genetically modified T-cells expressing a CD19 CAR, cryopreserved in an infusible grade cryomedium. UCART19 is defined as allogeneic engineered 19CAR/RQR8+_TCRαβ−_Tcells.
Follow-up period from D85 to M12. Then, 4 patients entered a separate LTFU study to be followed for 15 years. At cut-off, 2 patients withdrew due to progressive disease, 1 for adverse events. 1 patients is ongoing.

Arm type	Experimental
Investigational medicinal product name	UCART19
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Delivery of UCART19 was performed at D0 by intravenous infusion over approximately 5 minutes, following cell thawing in a 37°C bath. It is cryopreserved and supplied as a suspension for IV infusion conditioned in a primary container (1.8 mL cryovials) containing approximately 1 mL of a given dosage form of cell suspension.
A flat UCART19 dose per patient per dose level was initially developed, with a first dose of 6x106 UCART19/ patient (a flat dose stands for a number of CD19CAR/RQR8+_TCRαβ-_T-cells). The flat dose was developed to be administered to all patients, independently of their weight. The corresponding dose of cells expressed in a dose per kg was based on an average patient’s weight of 60 kg. As the use of partial vials is not recommended, patients enrolled at Dose level 1 (DL1) 1x 105 cells or DL-1 (1x 104) cells/kg received a flat dose not adjusted for weight. Weight band dosing was applied for DL2 (1x 106 cells/kg) and DL3 (3x 106 cells/kg).

Arm title	1E6 cells/kg

Arm description:

At D-7 , a LymphoDepletion (LD) was initiated. The LD treatment was the enhancement of homeostatic proliferation of the infused UCART19 cells by deep and prolonged depletion of host immune cells. It combined fludarabine 30 mg/m2/day IV, cyclophosphamide 500 mg/m2/day IV and alemtuzumab IV 0.2 mg/kg/day or 8 mg/day or 12 mg/day.
The treatment period started at time of UCART19 administration at D0 up to D84. UCART19 is a frozen suspension of allogeneic genetically modified T-cells expressing a CD19 CAR, cryopreserved in an infusible grade cryomedium. UCART19 is defined as allogeneic engineered 19CAR/RQR8+_TCRαβ−_Tcells.

Follow-up period from D85 to M12. Then, 9 patients entered a separate LTFU study to be followed for 15 years. At cut-off, 2 patients withdrew due to death, 1 for adverse events, 6 patients are ongoing.

Arm type	Experimental
Investigational medicinal product name	UCART19
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Delivery of UCART19 was performed at D0 by intravenous infusion over approximately 5 minutes, following cell thawing in a 37°C bath. It is cryopreserved and supplied as a suspension for IV infusion conditioned in a primary container (1.8 mL cryovials) containing approximately 1 mL of a given dosage form of cell suspension.
A flat UCART19 dose per patient per dose level was initially developed, with a first dose of 6x106 UCART19/ patient (a flat dose stands for a number of CD19CAR/RQR8+_TCRαβ-_T-cells). The flat dose was developed to be administered to all patients, independently of their weight. The corresponding dose of cells expressed in a dose per kg was based on an average patient's weight of 60 kg. As the use of partial vials is not recommended, patients enrolled at Dose level 1 (DL1) 1x 105 cells or DL-1 (1x 104) cells/kg received a flat dose not adjusted for weight. Weight band dosing was applied for DL2 (1x 106 cells/kg) and DL3 (3x 106 cells/kg).

Arm title	3E6 cells/kg

Arm description:

At D-7 , a LymphoDepletion (LD) was initiated. The LD treatment was the enhancement of homeostatic proliferation of the infused UCART19 cells by deep and prolonged depletion of host immune cells. It combined fludarabine 30 mg/m2/day IV, cyclophosphamide 500 mg/m2/day IV and alemtuzumab IV 0.2 mg/kg/day or 8 mg/day or 12 mg/day.
The treatment period started at time of UCART19 administration at D0 up to D84. UCART19 is a frozen suspension of allogeneic genetically modified T-cells expressing a CD19 CAR, cryopreserved in an infusible grade cryomedium. UCART19 is defined as allogeneic engineered 19CAR/RQR8+_TCRαβ–_Tcells.
Follow-up period from D85 to M12. Then, 4 patients entered a separate LTFU study to be followed for 15 years. At cut-off, 1 patient withdrew due to death, 1 for other reason. 2 patients are ongoing.

Arm type	Experimental
Investigational medicinal product name	UCART19
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Delivery of UCART19 was performed at D0 by intravenous infusion over approximately 5 minutes, following cell thawing in a 37°C bath. It is cryopreserved and supplied as a suspension for IV infusion conditioned in a primary container (1.8 mL cryovials) containing approximately 1 mL of a given dosage form of cell suspension.
A flat UCART19 dose per patient per dose level was initially developed, with a first dose of 6x106 UCART19/ patient (a flat dose stands for a number of CD19CAR/RQR8+_TCRαβ-_T-cells). The flat dose was developed to be administered to all patients, independently of their weight. The corresponding dose of cells expressed in a dose per kg was based on an average patient's weight of 60 kg. As the use of partial vials is not recommended, patients enrolled at Dose level 1 (DL1) 1x 105 cells or DL-1 (1x 104) cells/kg received a flat dose not adjusted for weight. Weight band dosing was applied for DL2 (1x 106 cells/kg) and DL3 (3x 106 cells/kg).

Number of subjects in period 1	1E5 cells/kg	1E6 cells/kg	3E6 cells/kg
Started	6	12	7
Completed	2	1	0
Not completed	4	11	7
Adverse event, serious fatal	-	-	1
Physician decision	2	5	3
Adverse event, non-fatal	1	1	2
Progressive disease	1	4	1
Non-medical reason	-	1	-

Reporting group values	Total		
Number of subjects	25		
Age categorical Units: Subjects			
Adults (18-64 years)	25		
Age continuous Units: years arithmetic mean standard deviation	 -		
Gender categorical Units: Subjects			
Female	11		
Male	14		

End points

End points reporting groups

Reporting group title	1E5 cells/kg

Reporting group description:

At D-7 , a LymphoDepletion (LD) was initiated. The LD treatment was the enhancement of homeostatic proliferation of the infused UCART19 cells by deep and prolonged depletion of host immune cells. It combined fludarabine 30 mg/m2/day IV, cyclophosphamide 500 mg/m2/day IV and alemtuzumab IV 0.2 mg/kg/day or 8 mg/day or 12 mg/day.
The treatment period started at time of UCART19 administration at D0 up to D84. UCART19 is a frozen suspension of allogeneic genetically modified T-cells expressing a CD19 CAR, cryopreserved in an infusible grade cryomedium. UCART19 is defined as allogeneic engineered 19CAR/RQR8+_TCRαβ−_Tcells.
Follow-up period from D85 to M12. Then, 4 patients entered a separate LTFU study to be followed for 15 years. At cut-off, 2 patients withdrew due to progressive disease, 1 for adverse events. 1 patients is ongoing.

Reporting group title	1E6 cells/kg

Reporting group description:

At D-7 , a LymphoDepletion (LD) was initiated. The LD treatment was the enhancement of homeostatic proliferation of the infused UCART19 cells by deep and prolonged depletion of host immune cells. It combined fludarabine 30 mg/m2/day IV, cyclophosphamide 500 mg/m2/day IV and alemtuzumab IV 0.2 mg/kg/day or 8 mg/day or 12 mg/day.
The treatment period started at time of UCART19 administration at D0 up to D84. UCART19 is a frozen suspension of allogeneic genetically modified T-cells expressing a CD19 CAR, cryopreserved in an infusible grade cryomedium. UCART19 is defined as allogeneic engineered 19CAR/RQR8+_TCRαβ−_Tcells.
Follow-up period from D85 to M12. Then, 9 patients entered a separate LTFU study to be followed for 15 years. At cut-off, 2 patients withdrew due to death, 1 for adverse events, 6 patients are ongoing.

Reporting group title	3E6 cells/kg

Reporting group description:

At D-7 , a LymphoDepletion (LD) was initiated. The LD treatment was the enhancement of homeostatic proliferation of the infused UCART19 cells by deep and prolonged depletion of host immune cells. It combined fludarabine 30 mg/m2/day IV, cyclophosphamide 500 mg/m2/day IV and alemtuzumab IV 0.2 mg/kg/day or 8 mg/day or 12 mg/day.
The treatment period started at time of UCART19 administration at D0 up to D84. UCART19 is a frozen suspension of allogeneic genetically modified T-cells expressing a CD19 CAR, cryopreserved in an infusible grade cryomedium. UCART19 is defined as allogeneic engineered 19CAR/RQR8+_TCRαβ−_Tcells.
Follow-up period from D85 to M12. Then, 4 patients entered a separate LTFU study to be followed for 15 years. At cut-off, 1 patient withdrew due to death, 1 for other reason. 2 patients are ongoing.

Primary: Best Overall Response (BOR): Complete Remission (CR) MRD negative

End point title	Best Overall Response (BOR): Complete Remission (CR) MRD negative[1]

End point description:

End point type	Primary

End point timeframe:

At D-1, D14, D28, D56, D84, M4, M6, M9 and M12 or at the WD visit.

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: Groups are too small

End point values	1E5 cells/kg	1E6 cells/kg	3E6 cells/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	12	7	
Units: no unit	0	1	1	

Statistical analyses

No statistical analyses for this end point

Primary: BOR: Complete remission incomplete blood count recovery (CRi) MRD negative

End point title	BOR: Complete remission incomplete blood count recovery (CRi) MRD negative[2]

End point description:

End point type	Primary

End point timeframe:

At D-1, D14, D28, D56, D84, M4, M6, M9 and M12 or at the WD visit.

Notes:

[2] - 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: Groups are too small

End point values	1E5 cells/kg	1E6 cells/kg	3E6 cells/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	12	7	
Units: no unit	3	4	0	

Statistical analyses

No statistical analyses for this end point

Primary: BOR: Morphologic CR/CRi

End point title	BOR: Morphologic CR/CRi[3]

End point description:

End point type	Primary

End point timeframe:

At D-1, D14, D28, D56, D84, M4, M6, M9 and M12 or at the WD visit.

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: Groups are too small

End point values	1E5 cells/kg	1E6 cells/kg	3E6 cells/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	12	7	
Units: no unit	0	0	2	

Statistical analyses

No statistical analyses for this end point

Primary: Dose Limiting Toxicity (DLT) and the Maximum Tolerated Dose (MTD)

End point title	Dose Limiting Toxicity (DLT) and the Maximum Tolerated Dose (MTD)[4]

End point description:

The MTD is defined as the highest dose at which the toxicity probability is the closest to the target probability of 0.3.

End point type	Primary

End point timeframe:

At D-1, D14, D28, D56, D84, M4, M6, M9 and M12 or at the WD visit.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The MTD was defined as the DL3 (3x106 cells/kg). According to DSMB meeting conclusion, the recommended dose was defined as the DL2 (1x106 cells/kg) based on several criteria: the acceptable safety profile, the greater level of UCART19 expansion and persistence in the patients receiving lymphodepletion with FCA at this dose level compared with DL1 and DL3 and the antileukemic activity of UCART19 at this dose in patients who were older or who had more aggressive disease.

End point values	1E5 cells/kg	1E6 cells/kg	3E6 cells/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	12	7	
Units: no unit	1	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: BOR: MRD indeterminate CR/CRi

End point title	BOR: MRD indeterminate CR/CRi

End point description:

End point type	Secondary

End point timeframe:

At D-1, D14, D28, D56, D84, M4, M6, M9 and M12 or at the WD visit.

End point values	1E5 cells/kg	1E6 cells/kg	3E6 cells/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	12	7	
Units: no unit	1	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

End point type	Secondary

End point timeframe:

At D-1, D14, D28, D56, D84, M4, M6, M9 and M12 or at the WD visit.

End point values	1E5 cells/kg	1E6 cells/kg	3E6 cells/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	12	7	
Units: no unit	4	7	2	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
All adverse events occurring from the LymphoDepletion to the end of follow-up.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21
Reporting groups	
Reporting group title	1E5 cells/kg
Reporting group description: -	
Reporting group title	3E6 cells/kg
Reporting group description: -	
Reporting group title	1E6 cells/kg
Reporting group description: -	

Serious adverse events	1E5 cells/kg	3E6 cells/kg	1E6 cells/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	7 / 7 (100.00%)	6 / 12 (50.00%)
number of deaths (all causes)	3	3	2
number of deaths resulting from adverse events	1	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia recurrent			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (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
Central nervous system leukaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Leukaemic infiltration extramedullary			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (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
Leukaemic infiltration renal			

subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
General disorders and administration site conditions			
Feeling hot			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 6 (33.33%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 2	1 / 1	0 / 0
Immune system disorders			
Acute graft versus host disease in skin			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (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
Cytokine release syndrome			
subjects affected / exposed	3 / 6 (50.00%)	4 / 7 (57.14%)	3 / 12 (25.00%)
occurrences causally related to treatment / all	3 / 3	4 / 4	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (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
Haemophagocytic lymphohistiocytosis			

subjects affected / exposed	0 / 6 (0.00%)	2 / 7 (28.57%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (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
Hypogammaglobulinaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung opacity			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (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
Pneumothorax			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (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
Pulmonary haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Pulmonary oedema			

subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (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
Respiratory failure			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (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
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (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
Anxiety			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (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
Confusional state			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychomotor retardation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
BK polyomavirus test positive			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (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
Blood creatinine increased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocyte count decreased			
subjects affected / exposed	2 / 6 (33.33%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental underdose			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (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
Acute haemolytic transfusion reaction			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (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
Infusion related reaction			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (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
Product administration error			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (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
Nervous system disorders			

Brain oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurotoxicity			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyramidal tract syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (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
Blood and lymphatic system disorders			
Bone marrow failure			
subjects affected / exposed	2 / 6 (33.33%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytopenia			
subjects affected / exposed	2 / 6 (33.33%)	2 / 7 (28.57%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 2	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	3 / 6 (50.00%)	2 / 7 (28.57%)	2 / 12 (16.67%)
occurrences causally related to treatment / all	1 / 4	1 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			

subjects affected / exposed	1 / 6 (16.67%)	2 / 7 (28.57%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 7 (28.57%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (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
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (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
Gastrointestinal inflammation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip swelling			
subjects affected / exposed	2 / 6 (33.33%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Swollen tongue			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (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

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (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
Cytomegalovirus infection reactivation			
subjects affected / exposed	1 / 6 (16.67%)	2 / 7 (28.57%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterobacter sepsis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterococcal infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterococcal sepsis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (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
Lower respiratory tract infection fungal			
subjects affected / exposed	0 / 6 (0.00%)	2 / 7 (28.57%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (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
Sepsis			

subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Septic shock			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Staphylococcal sepsis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Tumour lysis syndrome			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	1E5 cells/kg	3E6 cells/kg	1E6 cells/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	7 / 7 (100.00%)	12 / 12 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Precursor B-lymphoblastic lymphoma recurrent			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Vascular disorders			

Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Hypotension			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Raynaud's phenomenon			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Thrombophlebitis superficial			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Hypothermia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Oedema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	1 / 6 (16.67%)	3 / 7 (42.86%)	0 / 12 (0.00%)
occurrences (all)	1	3	0
Pyrexia			
subjects affected / exposed	2 / 6 (33.33%)	3 / 7 (42.86%)	5 / 12 (41.67%)
occurrences (all)	2	3	7
Swelling			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Acute graft versus host disease in skin			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Cytokine release syndrome			

subjects affected / exposed	3 / 6 (50.00%)	2 / 7 (28.57%)	7 / 12 (58.33%)
occurrences (all)	3	2	7
Hypogammaglobulinaemia			
subjects affected / exposed	2 / 6 (33.33%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hiccups			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hypoxia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Upper-airway cough syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Confusional state			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Disorientation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hallucination			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Insomnia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 6 (33.33%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	3	2	0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 6 (33.33%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	3	1	0
Blood bilirubin increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	2 / 12 (16.67%)
occurrences (all)	1	1	2
Blood creatinine increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 7 (28.57%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Blood immunoglobulin A decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood immunoglobulin M decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 6 (33.33%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	1
C-reactive protein increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Ejection fraction decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Eosinophil count increased			

subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
International normalised ratio increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Liver function test abnormal			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Neutrophil count decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	2
Oxygen saturation decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Platelet count decreased			
subjects affected / exposed	2 / 6 (33.33%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	3	0	1
Serum ferritin increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Weight decreased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Weight increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
White blood cell count decreased			
subjects affected / exposed	2 / 6 (33.33%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Injury, poisoning and procedural complications			

Head injury			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Infusion related reaction			
subjects affected / exposed	5 / 6 (83.33%)	4 / 7 (57.14%)	3 / 12 (25.00%)
occurrences (all)	10	4	3
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Sinus tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Ventricular tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Facial paralysis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	4 / 12 (33.33%)
occurrences (all)	0	1	4
Myoclonus			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Neurotoxicity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Paraesthesia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Peripheral sensory neuropathy			

subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Tension headache			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 6 (66.67%)	4 / 7 (57.14%)	6 / 12 (50.00%)
occurrences (all)	4	4	6
Lymphadenopathy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Neutropenia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Thrombocytopenia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 7 (28.57%)	3 / 12 (25.00%)
occurrences (all)	0	2	3
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Eye disorders			
Visual impairment			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Abdominal pain			
subjects affected / exposed	2 / 6 (33.33%)	1 / 7 (14.29%)	2 / 12 (16.67%)
occurrences (all)	2	1	2
Abdominal pain lower			

subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Constipation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Dental caries			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	3 / 6 (50.00%)	1 / 7 (14.29%)	2 / 12 (16.67%)
occurrences (all)	4	1	2
Dry mouth			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Flatulence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal wall thickening			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia oral			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	3 / 6 (50.00%)	3 / 7 (42.86%)	5 / 12 (41.67%)
occurrences (all)	4	3	6
Parotid gland enlargement			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Stomatitis			

subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	2 / 12 (16.67%)
occurrences (all)	1	0	2
Toothache			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Drug eruption			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Papule			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Petechiae			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Rash follicular			

subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Rash macular			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Toxic skin eruption			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Haematuria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)

subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Infections and infestations			
Adenovirus infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
BK virus infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Cellulitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Cytomegalovirus infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Cytomegalovirus infection reactivation			
subjects affected / exposed	2 / 6 (33.33%)	2 / 7 (28.57%)	0 / 12 (0.00%)
occurrences (all)	2	2	0
Escherichia bacteraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Herpes simplex			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Lip infection			

subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Metapneumovirus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Oral herpes			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	2 / 12 (16.67%)
occurrences (all)	1	0	3
Parainfluenzae virus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Tinea versicolour			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Fluid overload			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Hypercalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hypermagnesaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hypernatraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Hyperuricaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hypocalcaemia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 7 (28.57%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Hypokalaemia			
subjects affected / exposed	2 / 6 (33.33%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	1
Hypomagnesaemia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	4	1	0
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hypophosphataemia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 7 (14.29%)	1 / 12 (8.33%)
occurrences (all)	3	1	1
Vitamin D deficiency			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 November 2016	Amendment No. 1 applicable in all countries, mainly concerned: - Addition of information on the communication plan between Sponsor and all centres to ensure that when dose escalation or other stopping criteria were met at any site, the information was communicated to all sites immediately so that no patient received a dose that had been determined to be too toxic. - Modification of the original methodology of dose allocation into an mTPI design. - Modification of the statistical paragraph and analyses to be consistent along the protocol (response rate, duration of response, time to response, disease-specific survival and progression-free survival). - Addition of MTD to the primary objective. - Assessment of the objective response along the study (D84) was moved from the exploratory objectives to the secondary objectives; Overall response was added to the secondary objectives. - Modification of the definitions of the DLT Criteria. - Modification of the suggested lymphodepletion regimen to align with the lymphodepletion treatment suggested in the UCART19 paediatric protocol (UCART19- PALL Study). - Clarification on MRD methods of measurement: flow cytometry and/or qPCR could be used. - Modification of the adverse events definition. - Deletion of genotoxicity from the list of AESI. - Qualification of CALM study as a First-In-Human Study in adults.
11 January 2017	Amendment No. 2, applicable in all countries, to implement the recommendations received before the submission of the CALM study to the regulatory authorities in United States (US). The recommendations were mainly related to patient safety. The main changes included: - Modification of the flat dosing strategy and rationale to implement a weight-banded dosing strategy in selected cohorts (2 weight-bands). - Modification of the definitions of the DLT criteria including: * addition of any Grade ≥ 3 non-haematologic toxicity not resolving within 7 days, * down-grading of the GvHD to Grade ≥ 2 requiring oral or IV corticosteroids (> 1 mg/kg/day) and that does not resolve within 7 days, * removal of electrolyte abnormalities. - Addition of grading scale for TLS management. - Amendment of grading scale for acute GvHD to the grading of Harris. - Update on the management of safety risks and supportive care measures for CRS and neurotoxicity. - Addition of discontinuation criteria for using alemtuzumab in lymphodepletion regimen. - Addition on follow-up and management of chronic GvHD post UCART19 administration. - Surveillance/prophylaxis (viral, fungal, bacterial) was pursued for at least 1 year post UCART19 administration in patients receiving alemtuzumab. - Addition of immunogenicity assays (presence of anti-UCART19 antibodies) at D0, D28 and D84. - Modifications in the statistical paragraph, with addition of a minimum number of 3 patients to be dosed per each dose level tested in the mTPI design; addition of appendix 9. - Addition of one time point at D-7 (before the start of the lymphodepletion treatment) for UCART19 analysis by flow cytometry. - Assessment of CD52 expression on leukemic blasts (on blood/bone marrow if assessments were performed locally). - Assessment of the percentage of CD19-positive and CD19-negative leukaemia cells in bone marrow, if the assessment was performed locally.

02 March 2017	-Amendment No. 3, applicable in all countries to implement the requests received by the US regulatory authorities (Food and Drug Administration) after the Investigational New Drug review. The recommendations were only related to patients' safety. The main changes included: - Implementation of a dose expansion phase. - Definition of treatment pause rules. - Modification of the definition of the DLT criterion for nervous system disorders: Grade ≥ 3 lasting more than 7 days (instead of 14 days) or Grade ≥ 4. - Removal of one exploratory objective (patients planned for allo-HSCT). - Assessment of cytokines in the frame of a CRS reaction, if performed locally. - Statistics part updated with definition of treatment pause rules, addition of a dose expansion phase with 2 different lymphodepletion regimens, deletion of exploratory criteria and determination of sample size.
22 March 2018	-Amendment No. 4, applicable in all countries. One of the main objectives of this substantial amendment was to include the possibility to re-dose the patient with UCART19. The main changes included: - Addition of a section defining criteria for an optional UCART19 re-dosing after the initial UCART19 infusion. - Extension of the study duration to 13 months and modification of the study plan (definition of treatment and follow-up periods). - Addition of a new important potential risk identified of prolonged cytopenia. - Modification of the dose of alemtuzumab in the lymphodepletion treatment. - Addition of criteria defining a patient not evaluable for DLT. - Update of the "treatments prohibited" and "treatments authorised". - Update of safety risks: CRS, neurologic toxicity and genotoxicity. - Update of the time points of disease assessment. - Update of the safety assessments during the treatment and follow-up periods, definition of a new AESI (prolonged neutropenia), addition of a mandatory neurological consultation in France during the screening period (adapted to local practices for other countries). - Update of the exploratory analyses. - Update of the statistics part: adaptation of secondary objectives and efficacy endpoints to the extended study duration of 13 months, clarifications regarding the number of patients treated in the safety expansion part, modifications of the data analysis sets.
25 April 2019	-Amendment No. 6, applicable in all countries. The first main objective of this substantial amendment was to assess the FCA regimen as lymphodepleting regimen prior to UCART19 infusion in the next patients included in the CALM study. Whatever the moment the patient entered in CALM (dose-escalating part or safety dose expansion part), the use of alemtuzumab at the dose of 40 mg (8 mg/kg/day for 5 days) became mandatory for all patients. The main changes concerned: - Update of study design, study plan and the safety dose expansion procedure removing the FC arm in the safety dose-expansion part. - Update of lymphodepletion regimen with possibility to increase alemtuzumab dose to 60 mg flat dose. - Modification of the total number of patients treated (from 40 patients initially to 30 patients). - Addition of the primary objective concerning the safety dose expansion part. - Removal of soluble CD52 in the exploratory endpoints. - Revision of DLT definition of nervous system disorder for UCART19. - Update of prohibited and authorized treatments. - Clarifications of the AE of special interest per study period. - Clarifications of the time frame for AE reporting. - Clarification on DSMB role at the end of the study. - Addition of checking of DSAs directed against UCART19 before any re-dosing. - Clarification on UCART19 assessment in case of neurotoxic event.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported