Clinical trial results:
A phase 1, open label, non-comparative, study to evaluate the safety and the ability of UCART19 to induce molecular remission in paediatric patients with relapsed /refractory B-cell acute lymphoblastic leukaemia

Summary

EudraCT number	2015-004293-15
Trial protocol	GB BE FR ES
Global end of trial date	04 November 2020

Results information

Result version number	v1 (current)
This version publication date	19 May 2021
First version publication date	19 May 2021

Trial information

Trial identification

Sponsor protocol code	UCART19_02 (CL1-68587-001)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02808442
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	17 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 September 2020
Global end of trial reached?	Yes
Global end of trial date	04 November 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of UCART19 in paediatric patients with relapsed or refractory (R/R) B-ALL.

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	03 June 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	United Kingdom: 6
Country: Number of subjects enrolled	United States: 5
Country: Number of subjects enrolled	France: 2
Worldwide total number of subjects	13
EEA total number of subjects	2

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)	3
Children (2-11 years)	5
Adolescents (12-17 years)	5
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Male or female patients aged < 18 years, with R/R CD19-positive B-ALL, as per National Comprehensive Cancer Network guidelines, 2020:
Morphologically confirmed with ≥ 5% leukemic blasts in the bone marrow or presenting a quantifiable Minimal Residual Disease (MRD) load of 1x10-3 and/or quantitative polymerase chain reaction (qPCR).

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

Arm title	UCART19

Arm description:

At D-4 , a LymphoDepletion (LD) was initiated. The LD regimen was modified by amendments (see below). The final combination was fludarabine 30 mg/m2/day IV over 15/30 minutes from D-4 to D-2 (90 mg/m² total dose), cyclophosphamide 800 mg/m²/day over 1 hour from D-3 to D-2 (1600 mg/m² total dose) and alemtuzumab 0.3 mg/kg at D-4, 0.3 mg/kg at D-3 and 0.4 mg/kg at D-2 [1mg/kg capped at 40 mg (total dose)].
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 an allogeneic engineered 19CAR/RQR8+_TCRαβ−_T-cells.
Follow-up period (FU): D85 to M12.
At FU end, 7 patients entered a separate LTFU study to be followed for 15 years and 6 patients did not : 5 for death and 1 for investigator decision. At cut-off in the LTFU, 1 patient withdrew due to progressive disease, 3 due to death. 3 patients are ongoing.

Arm type	Experimental
Investigational medicinal product name	UCART19
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
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.
All patients received a dose of 1 to 3x106/kg CD19CAR/RQR8+_TCRαβ-_T-cells.

Number of subjects in period 1	UCART19
Started	13
Completed	2
Not completed	11
Physician decision	3
Death	3
Progressive disease	5

Baseline characteristics

Reporting groups	
Reporting group title	Overall study period

Reporting group description: -

Reporting group values	Overall study period	Total	
Number of subjects	13	13	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	3	3	
Children (2-11 years)	5	5	
Adolescents (12-17 years)	5	5	
Age continuous Units: years			
arithmetic mean	7.39		
standard deviation	± 6.44	-	
Gender categorical Units: Subjects			
Female	6	6	
Male	7	7	

End points

End points reporting groups

Reporting group title	UCART19

Reporting group description:

At D-4 , a LymphoDepletion (LD) was initiated. The LD regimen was modified by amendments (see below). The final combination was fludarabine 30 mg/m2/day IV over 15/30 minutes from D-4 to D-2 (90 mg/m² total dose), cyclophosphamide 800 mg/m²/day over 1 hour from D-3 to D-2 (1600 mg/m² total dose) and alemtuzumab 0.3 mg/kg at D-4, 0.3 mg/kg at D-3 and 0.4 mg/kg at D-2 [1mg/kg capped at 40 mg (total dose)].
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 an allogeneic engineered 19CAR/RQR8+_TCRαβ−_T-cells.
Follow-up period (FU): D85 to M12.
At FU end, 7 patients entered a separate LTFU study to be followed for 15 years and 6 patients did not : 5 for death and 1 for investigator decision. At cut-off in the LTFU, 1 patient withdrew due to progressive disease, 3 due to death. 3 patients are ongoing.

Primary: Incidence and Severity of Adverse Events

End point title	Incidence and Severity of Adverse Events[1]

End point description:

Adverse events assessed according to NCI-CTCAE v5.0 criteria (See Adverse Events Section)

End point type	Primary

End point timeframe:

From inclusion to Month 12

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: Only one group of treatment.

End point values	UCART19			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: no unit	13			

Statistical analyses

No statistical analyses for this end point

Secondary: Molecular Remission Rate

End point title	Molecular Remission Rate

End point description:

Proportion of patients in whom a molecular Complete Remission (CR) or a Complete Remission with incomplete blood recovery (CRi) is observed (i.e. a CR or CRi combined to a Minimal residual disease <10-4).

End point type	Secondary

End point timeframe:

At Day 28 after the first UCART19 infusion

End point values	UCART19			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: no unit	5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Emergent adverse events during treatment period were defined as adverse events that occurred or worsened (in terms of severity) or became serious between the first IMP intake date and the last IMP intake + 30 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	UCART19

Reporting group description: -

Serious adverse events	UCART19		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia recurrent			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Leukaemic infiltration extramedullary			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant neoplasm progression			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Hypertension			

subjects affected / exposed	2 / 13 (15.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Physical deconditioning			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Acute graft versus host disease in intestine			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute graft versus host disease in skin			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Cytokine release syndrome			
subjects affected / exposed	10 / 13 (76.92%)		
occurrences causally related to treatment / all	10 / 10		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Penile erythema			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Penile swelling			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary hypertension			

subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Disorganised speech				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hallucination				
subjects affected / exposed	2 / 13 (15.38%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Irritability				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Major depression				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Activated partial thromboplastin time prolonged				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood fibrinogen decreased				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
International normalised ratio increased				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

JC polyomavirus test positive				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutrophil count decreased				
subjects affected / exposed	2 / 13 (15.38%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
White blood cell count decreased				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Airway complication of anaesthesia				
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 reaction				
subjects affected / exposed	4 / 13 (30.77%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac arrest				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinus bradycardia				
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			
Cerebral haemorrhage			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chorea			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dysarthria			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dyskinesia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intraventricular haemorrhage			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lethargy			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neurotoxicity			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Posterior reversible encephalopathy			

syndrome				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cytopenia				
subjects affected / exposed	4 / 13 (30.77%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	2 / 13 (15.38%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	5 / 13 (38.46%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	2 / 13 (15.38%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Thrombotic microangiopathy				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Gastrointestinal disorders				

Abdominal pain				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mouth haemorrhage				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Gallbladder oedema				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Periportal oedema				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Ecchymosis				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Petechiae				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				

subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cystitis haemorrhagic			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal haematoma			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urethral obstruction			
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			
Muscle twitching			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Adenoviral 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		
Adenovirus infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

BK virus infection				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacterial sepsis				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cystitis viral				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus infection				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus infection reactivation				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fungal infection				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metapneumovirus infection				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary mucormycosis				

subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Streptococcal sepsis				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral haemorrhagic cystitis				
subjects affected / exposed	2 / 13 (15.38%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Fluid overload				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoalbuminaemia				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypocalcaemia				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	3 / 13 (23.08%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Hypophosphataemia				
subjects affected / exposed	2 / 13 (15.38%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Tumour lysis syndrome				

subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	UCART19		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 13 (92.31%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
General disorders and administration site conditions			
Face oedema			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	4		
Immune system disorders			
Acute graft versus host disease in skin			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Cytokine release syndrome			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Hypogammaglobulinaemia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Reproductive system and breast disorders			

Acquired phimosis subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) Hypoxia subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Pulmonary oedema subjects affected / exposed occurrences (all) Tachypnoea subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1		
Psychiatric disorders Confusional state subjects affected / exposed occurrences (all) Delirium subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all) Disorientation subjects affected / exposed occurrences (all)	 3 / 13 (23.08%) 3 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1		
Investigations Activated partial thromboplastin time prolonged subjects affected / exposed occurrences (all)	 2 / 13 (15.38%) 2		

Alanine aminotransferase increased				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Aspartate aminotransferase increased				
subjects affected / exposed	2 / 13 (15.38%)			
occurrences (all)	2			
Blood bilirubin increased				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Blood creatinine increased				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
International normalised ratio increased				
subjects affected / exposed	3 / 13 (23.08%)			
occurrences (all)	4			
Lymphocyte count decreased				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Neutrophil count decreased				
subjects affected / exposed	2 / 13 (15.38%)			
occurrences (all)	2			
Platelet count decreased				
subjects affected / exposed	2 / 13 (15.38%)			
occurrences (all)	2			
Prothrombin time prolonged				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Serum ferritin increased				
subjects affected / exposed	3 / 13 (23.08%)			
occurrences (all)	3			
Weight increased				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
White blood cell count decreased				

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Infusion related reaction			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Skin wound			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Ataxia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Lethargy			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Neurotoxicity			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Speech disorder			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 13 (38.46%)		
occurrences (all)	6		
Splenomegaly			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Gastrointestinal inflammation			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Haematemesis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Mouth haemorrhage			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Urinary ascites			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Rash macular			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Infections and infestations			
BK virus infection			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Coronavirus infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Cytomegalovirus infection reactivation			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Oral herpes			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Viral haemorrhagic cystitis			

subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hyperkalaemia subjects affected / exposed occurrences (all) Hypocalcaemia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hypophosphataemia subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 6 / 13 (46.15%) 8 2 / 13 (15.38%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2016	Amendment N°1, applicable in all countries, mainly concerned: - Modification of the definitions of "Criteria for defining toxicity". - Removal of inclusion criterion n°8 requesting the patients to consent in the same time to their participation to the parent study and to the LTFU study and addition of an exclusion criterion (criterion n°34) for patients who were unable or unwilling to undergo a safety follow-up for 15 years. - Clarification regarding the maximum amount of blood to be taken from participants. Reduction in time interval between inclusion of the 3rd and the 4th patient and thereafter between inclusion of 2 consecutive patients within a group of 3 patients. - Addition of a communication plan between sponsor and sites. - Addition of exclusion criteria n° 33 (patients tested positive for HIV). - Clarification regarding exclusion criteria n°11 (reduction of the washout period required after the use of previous treatment). - Addition of reporting of CD52 expression data on leukemic cells as exploratory objective.
24 February 2017	Amendment N°2, applicable in all countries, mainly concerned: - Clarification of AEs to be reported during the FU period and deletion of Appendix 2. - Several modifications to be consistent with the safety changes implemented in the CALM protocol following Food and Drug Administration request and NIH recombinant DNA advisory Committee: * Modification of the definitions of "Criteria for defining toxicity". * Use of the grading of Harris (Harris et al, 2016) for grading scale for GvHD. * Update on the management of safety risks and supportive care measures; addition of appendices "CRS management" and "neurotoxicity management". * Addition of ineligibility criteria for using alemtuzumab in LD regimen. * Addition of discontinuation criteria for using alemtuzumab in LD regimen. * Recommendation for antimicrobial surveillance/prophylaxis for opportunistic infections (viral, fungal, bacterial) until blood count recovery for patients receiving alemtuzumab. * Addition of one blood sample for potential retrospective genomic analysis in case of T-cell transformation, at D0, D84, M6 and M12. * Addition of immunogenicity assays (human anti-UCART19 antibodies) at D0, D28, D84 and M12. - Rewording of exclusion criteria n° 24 to define more specifically an active infection. - Addition of eligibility criteria before UCART19 administration in the study plan. - Modification of the exclusion criteria n°33 with the exclusion of patients tested positive for HTLV at inclusion. - Addition of IL4 in the list of parameters to be dosed among the cytokines. - Reporting in the eCRF of data on CD52 expression on leukemic blasts (on blood or bone marrow if assessments were performed locally).

23 November 2017	Amendment N°3, applicable in all countries, mainly concerned: - To discontinue the use of alemtuzumab following DSMB recommendation. - To modify the doses of fludarabine-cyclophosphamide used as part of LD regimen. - To implement the request received from the ANSM after the submission of PALL and CALM protocols: - Addition of the inclusion criterion n°35 (list of biological parameters and clinical parameters with limit values to be checked). - Deletion of the exclusion criterion n°23 ("Unstable cardiovascular disease", replaced by clinical parameters of cardiac function as part of the inclusion criterion n°35). - Addition of the exclusion criterion n°36 ("Any known contraindication to any of the drugs that will be used for the lymphodepletion (fludarabine, cyclophosphamide) or other drugs proposed for safety issues (including tocilizumab, rituximab)"). - Addition of a neurological consultation (mandatory for France and according to local practices for other countries) during the screening period. - Addition of cytoreduction decision criteria. - Addition of an immunoglobulin assay at D14 (if required). - Update of paragraph on neurotoxicities and its corresponding appendix. - Update of appendix "CRS mitigation and management".
28 February 2018	Amendment N°4, applicable in all countries, mainly concerned: - To remove the planned allo-HSCT from the study protocol, with update of study objectives. - To add the possibility of an optional UCART19 re-dosing after the initial UCART19 infusion. - To modify the study duration from 15 months to 12 months and to modify the study plan with the definition of treatment and follow-up periods. - To add 8 participants (up to 18 participants) and consequently to modify the stopping rules and to define the enrolment strategy from the 10th patient. - To clarify the safety risks (CRS, neurologic toxicity and genotoxicity and tumorigenicity). - To add a new safety identified risk, prolonged cytopenia. - To add "prolonged cytopenia" as new AESI to be considered during the treatment period. - Addition of an eligibility criterion n°44 "Availability of a donor for potential allo-HSCT in the event of persistent marrow aplasia without evidence of residual leukaemia".
17 August 2018	Amendment N°6, applicable in all countries. The main objective of this amendment was to re-introduce the use of alemtuzumab in the lymphodepletion regimen following DSMB recommendation. Accordingly, the following changes were applied: - Re-introduction of ineligibility criteria and stopping rules for alemtuzumab administration. - Modification of the doses of fludarabine and cyclophosphamide when administered in combination with alemtuzumab. - Modification of exclusion criteria n°36 to include alemtuzumab. - Modification of treatment authorized to include methylprednisolone and surveillance/prophylaxis measures in case of alemtuzumab use. - Modification of safety risks and supportive care measures for infection in case of alemtuzumab use. - Update of assessment of safety to include the addition of surveillance/prophylaxis measures in case of alemtuzumab use in viral/bacterial/protozoal work-up.

26 March 2019	Amendment N°8, applicable in all countries. The main objectives of this substantial amendment were: - To modify some inclusion and exclusion criteria in order to address a high unmet medical need for some categories of patients: - Update of inclusion criterion n°2 with the inclusion of patients from birth. - Addition of inclusion criterion n°60 (no detectable anti-CD19 CAR transgene copies in blood, by qPCR, in patients previously treated with CAR T cell therapy). - Update of exclusion criterion n°10 (with the addition of the exception "autologous CAR-T cell therapy"). - Addition of exclusion criterion n°61 (known history of CRS grade 4 related to previous CAR T cell therapy). - Removal of exclusion criterion n°14 (weight below 8.8 kg). - Update of exclusion criterion n°16a (with exclusion of patients with allogeneic HSCT within 3 months prior to screening instead of 6 months). - Update of exclusion criterion n°29 (which became "known history of irreversible severe neurological toxicity related to previous antileukemic treatment leading to organic central nervous system lesions"). - To update the dose of CD19CAR/RQR8+_TCRαβ-_T-cells/kg resulting from the weight band dosing calculation.
23 January 2020	Amendment N°9, applicable in all countries. The main objectives were: - To modify LD regimen schedule: start lymphodepletion at D-4 and modifications of doses of cyclophosphamide and alemtuzumab. - To modify some exclusion/inclusion criteria: update of inclusion criteria 35a, 38a, 53a with serum ALT/ AST ≤ 5 times ULN instead of 3 times ULN; update of inclusion criterion n°60 with the addition of B cells recovery as surrogate demonstrating the loss of CAR T cells persistence and update of exclusion criterion n°59 to allow use of corticosteroids in combination with alemtuzumab at D-4 and D-3. - To modify eligibility criteria for UCART19 (re)-administration: deletion of criteria 41a and 56 concerning disease progression after lymphodepletion. - To clarify the use of alemtuzumab: update of the use of alemtuzumab as non-optional, update of the stopping rules for the use of alemtuzumab and addition of exclusion criteria related to use of alemtuzumab (criterion n°62). - To allow re-dosing possibility from D14 instead of D28 (update of criteria n°46 and 47). - And to update AESI immediate reporting rules (only severe and/ or serious events to be notified immediately).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
04 November 2020	The study was terminated as sponsor reviewed its development strategy and decided to stop the development of S68587 in the indication of R/R B ALL. This decision was not due to safety concerns.	-

Notes:

Limitations and caveats

None reported