

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 $\geq 5\%$ 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 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+_TCR $\alpha\beta$ -_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+_TCRa β -_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 title	TOVERALL SLUCY DELICO

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	

EU-CTR publication date: 19 May 2021

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)].

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Primary: Incidence and Severity of Adverse Events

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

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 extramedullar	y	
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 / 12 /7 (00/)	1	
	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			ĺ
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	İ	İ
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	

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occurrences causally related to treatment / all	-	1 / 13 (7.69%)		
deaths causally related to treatment / all 0 / 0				
Posterior reversible encephalopathy	deaths causally related to	0/0		
	Posterior reversible encephalopathy		İ	İ

syndrome	1	1	1
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		
	l	<u> </u>	
Gastrointestinal disorders	0/1		

	1		
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		j i	ĺ
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	1	
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	

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	I]
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	İ		
1	1	ı	ı

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	1 / 13 (7.69%)	
occurrences (all)	1	
Respiratory, thoracic and mediastinal		
disorders		
Epistaxis		
subjects affected / exposed	1 / 13 (7.69%)	
occurrences (all)	1	
Нурохіа		
subjects affected / exposed	1 / 13 (7.69%)	
occurrences (all)	1	
	_	
Pleural effusion		
subjects affected / exposed	1 / 13 (7.69%)	
occurrences (all)	1	
Dulmanama and man		
Pulmonary oedema subjects affected / exposed	1 / 12 /7 (00/)	
	1 / 13 (7.69%)	
occurrences (all)	1	
Tachypnoea		
subjects affected / exposed	1 / 13 (7.69%)	
occurrences (all)	1	
Psychiatric disorders Confusional state		
subjects affected / exposed	3 / 13 (23.08%)	
occurrences (all)		
occurrences (un)	3	
Delirium		
subjects affected / exposed	1 / 13 (7.69%)	
occurrences (all)	1	
Depression		
subjects affected / exposed	1 / 13 (7.69%)	
occurrences (all)	1	
Disorientation		
subjects affected / exposed	1 / 13 (7.69%)	
occurrences (all)	1	
Investigations		
Activated partial thromboplastin time prolonged		
subjects affected / exposed	2 / 13 (15.38%)	
occurrences (all)	2	

Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 13 (7.69%)		
Aspartate aminotransferase increased subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Blood bilirubin increased subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Blood creatinine increased subjects affected / exposed	1 / 13 (7.69%)		

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		

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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 (42 (45 222 ()		
	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	l	l	

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)			
occurrences (air)	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		
(4)	1		
Musculoskeletal and connective tissue			
disorders Muscular weakness			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)			
occurrences (air)	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		
occan enece (any	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)			
Coodinations (un)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Viral haemorrhagic cystitis			

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

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. * 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).

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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+_TCRαβT-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
	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