2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France **Local Sponsors:** Servier Research & Development Ltd, Sefton House - Sefton Park - Bells Hill - Stoke Poges - Buckinghamshire, SL2 4JS - United Kingdom Servier Canada Inc, 235 Boulevard Armand Frappier - Laval, QC H7V 4A7 - Canada	*(For National Authority Use only)*

Test drug
Name of Finished Product:
Not applicable
Name of Active Ingredient:
UCART19 (CD19CAR/RQR8+ _TCRαβ- _T-cells) (S68587)

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Title of study: 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)

Protocol No.: CL1-68587-002
EudraCT No.: 2016-000296-24

The description of the study protocol given hereafter includes the modifications of the 9 substantial amendments to the protocol applicable in all countries.

International coordinator or **National coordinator** or **Investigator**

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Study centres:
In all, 8 centres in 4 countries included 25 patients:
- 11 patients in United Kingdom (2 centres).
- 6 patients in France (2 centres).
- 6 patients in United States (2 centres).
- 2 patients in Japan (2 centres).

Publication (reference):
Benjamin R, Graham C, Yallop D, Jozwik A, Mirci-Danicar OC, Lucchini G, *et al*. Genome-edited, donor-derived allogeneic anti-CD19 chimeric antigen receptor T cells in paediatric and adult B-cell acute lymphoblastic leukaemia: results of two phase 1 studies. Lancet 2020; 396(10266):1885-1894.

Studied period: Initiation date: 10 August 2016 Completion date: 28 July 2020	**Phase of development of the study:** Phase I (first-in-human study in adults)

Objectives:
Primary objectives
The primary objectives of the study were:

- To assess the safety and tolerability of ascending doses of UCART19 given as a single infusion in patients with relapsed /refractory (R/R) ALL, 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 of UCART19 during the safety dose expansion part.

Secondary objectives
The secondary objectives were to assess the anti-leukemic activity of UCART19 throughout the study, specifically with:

- Rate of objective response at Day (D) 28, D84, Month (M) 4, M6, M9 and M12 after the first UCART19 infusion, and overall response.

- Duration of remission, time to remission, overall survival and progression-free survival after the first UCART19 infusion.

An objective response is defined as: (1) a molecular response (minimal residual disease (MRD) < 10^{-4} post treatment) assessed by multiparameter flow cytometry (FLC) and/or quantitative polymerase chain reaction (qPCR) or (2) a morphologic complete response or (3) a complete response with incomplete blood count recovery based on National Comprehensive Cancer Network (NCCN) guidelines.

Exploratory objectives

-   To assess the proportion of patients who underwent allogeneic haematopoietic stem cell transplantation (HSCT) following UCART19 infusion.

-   To assess the proportion of patients who underwent a re-dosing with UCART19.

-   To analyse the expansion, phenotype, trafficking and persistence of UCART19, by assessing the cellular kinetic profile of UCART19 and by characterising various UCART19 cell subsets at different time-points.

-   To characterise the pharmacokinetics (PK) profile of alemtuzumab and assess the potential immunogenicity directed against alemtuzumab.

-   To assess cytokine release and C-reactive protein levels.

-   To investigate the potential development of an anti-UCART19 immune response.

-   To monitor host immune cell depletion and reconstitution resulting from the lymphodepletion and UCART19 treatments.

-   To assess the potential switch of CD19 expression on patient's leukaemia cells.

-   To assess CD52 expression on patient's leukaemia cells.

-   To monitor the absence of replication competent lentivirus (RCL).

-   To identify specific gene expression signatures potentially associated with UCART19 expansion, efficacy and/or persistence.

-   To perform a retrospective genomic analysis, in case a T-cell transformation is observed.

Optional collection of biological samples (biocollection)
To collect blood and, if applicable, bone marrow samples for further analysis of safety and/or efficacy biomarkers (BMK) in patients who consented.

Methodology:

This was an international, multicentre, open-label, dose-escalating, first in human study of UCART19 in patients with R/R CD19 positive B-ALL. Patients were to be allocated to treatment in the order in which they were enrolled. This study was designed in two parts: a dose escalation part, followed by a safety dose expansion part.

The dose escalation part followed a modified Toxicity Probability Interval (mTPI) design based on the occurrence of Dose Limiting Toxicities (DLTs) after the first UCART19 administration. Four UCART19 dose levels could be tested with a minimum of 3 patients treated at a previously untested dose level. If a DLT was observed or upon decision of the data safety monitoring board (DSMB), 2 to 4 additional patients could be included at the same dose level. Escalation to the next ascending dose level or de-escalation to a dose level below or the inclusion of additional patients at the same dose level was performed upon DSMB recommendations in order to determine the MTD. The DSMB evaluated each DLT profile or the frequency and severity of DLTs in the same patient. The DSMB reviewed the safety data from each dose level after all patients in the cohort had completed the D28 visit post-dose. Any other relevant information coming from all patients included so far in the study could be combined by the DSMB to the mTPI recommendation to decide the next dose and to determine the MTD. To declare the MTD, at least 6 patients should be enrolled into a dose level.

A DLT was defined as an adverse event (AE) (excluding anorexia and fatigue) or an abnormal laboratory value occurring within the first 4 weeks (up to D28) following the first UCART19 administration, assessed as unrelated to leukaemia, intercurrent illness or concomitant medications, considered as related to the investigational medicinal product (IMP) by the investigator and which met any of the pre-established criteria.

For the safety dose expansion part, the MTD or a lower dose previously tested could be used. This dose of UCART19 was defined as the RD.

The LD regimen used was a combination of fludarabine, cyclophosphamide +/- alemtuzumab (FCA).

The aim of the **safety dose expansion part** was to confirm the safety and tolerability of the RD of UCART19. To this end, a cohort of at least 6 patients (and up to 12 patients if more safety, efficacy and PK data were needed to better characterise the safety profile of UCART19) were to be treated. Patients received the combination of FCA as LD regimen (before Amendment No.6, patients could receive only FC).

At the end of the safety dose expansion part, all safety, efficacy and exploratory data from the dose escalation and safety expansion parts were evaluated jointly by the DSMB members, investigators and the Sponsor to confirm the safety and tolerability of the RD for UCART19.

The study was divided into the following periods for each patient:
Screening period/Inclusion:
Before entering in the study protocol and according to their tumour burden and the investigator's judgement (not a requirement of the protocol), patients could receive a dexamethasone-based cytoreductive treatment as part of the routine care that should be completed before D-7 (initiation of lymphodepletion regimen). After signature of the Informed Consent Form, patients entered the screening period during which the eligibility criteria were checked, and the disease status was assessed on the bone marrow. In the same time, patients were encouraged to participate in the long-term follow-up (LTFU) study after completion or premature withdrawal from the CALM study.

Lymphodepletion treatment period (C000 period): from D-7 to D-1 prior to UCART19 infusion
The LD regimen was a combination of FCA (before Amendment No.6, patients could receive only FC). Patients could be hospitalised, according to the local practices per country, from 7 days before the administration of UCART19 (D-7) or the day before UCART19 administration (D-1). At the end of the LD regimen, eligibility criteria allowing UCART19 administration should be assessed within 24 hours prior to infusion in order to ensure patients' safety and a bone marrow aspiration was to be performed on D-1, in order to determine the tumour burden as close as possible to UCART19 infusion.

Treatment period: from D0 (UCART19 infusion) to D84 post-UCART19 infusion
Status of infection should be evaluated before UCART19 dosing. If an active infection not controlled by adequate treatment was detected after the start of the lymphodepletion, dosing could be delayed up to 21 days following the last day of the lymphodepletion treatment.
On D0, patients received a single intravenous (IV) dose of UCART19.

Follow-up (FU) period: from D85 to M12
This period could last 9 months. Patients were monitored at a hospital/ambulatory care unit on M4, M6, M9 and M12.

End of study (EOS) visit or withdrawal (WD) visit
The EOS visit was at M12 after the first UCART19 infusion. After completion of EOS /WD visit (complete evaluation), patients were immediately rolled-over to a 15-year follow-up period under a separate LTFU protocol.

UCART19 redosing (optional)
From D28 to M9 after the first UCART19 infusion, the possibility to re-dose a patient with UCART19 (second or third dose) might be discussed according the criteria of re-administration. Patients then started a new cycle starting from the LD (D-7) until 3 months after re-dosing (D84) and followed the same schedule of visits and assessments as described for the initial UCART19 infusion. At the end of the treatment period (D84) after the last UCART19 infusion, the patient switched to the next visit in the follow-up period scheduled in the study plan, corresponding to the time elapsed between the first dosing (*i.e.*, initial D0) and 84 days after the re-dosing.
Re-dosing could not occur after M9 and no more than 3 UCART19 infusions were allowed in the study period.

This study was performed in strict accordance with Good Clinical Practice.

The study has been completed but the 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. Therefore, the present clinical study report is abbreviated.

Number of patients:

Planned: 30 patients maximum, with:

- Up to 18 patients in the dose escalation part (cohort minimum size of 3 evaluable patients treated at a previously untested dose level, then 2 to 4 evaluable patients included per dose cohort at the same dose level, if applicable, and at least 6 patients treated at the MTD).

- And at least 6 patients and up to 12 patients treated at the RD, in the safety dose expansion part.

Included: 25 included patients with 19 patients in the dose escalation phase (6 patients in the UCART19 1×10^5 cells/kg group, 6 in the UCART19 1×10^6 cells/kg group and 7 in the UCART19 3×10^6 cells/kg group) and 6 in the safety dose expansion phase (all in the UCART19 1×10^6 cells/kg group).

Diagnosis and main criteria for inclusion:

Patients were male or female participants aged $\geq$ 16 years, up to < 70 years old, with R/R CD19+ B-ALL, as per NCCN guidelines, 2019:

- Morphologically confirmed with $\geq$ 5% leukemic blasts in the bone marrow.

- or presenting a quantifiable MRD load $\geq 1\times10^{-3}$, assessed by multiparameter FLC and/or qPCR, at the end of the last induction treatment.

- Who had exhausted alternative treatment options.
  Relapsed disease was defined as second or subsequent bone marrow relapse or, any bone marrow relapse after allo-HSCT.
  Refractory disease was defined by not achieving an initial complete response after 2 cycles of a standard chemotherapy regimen (primary refractory). Patients who were refractory to subsequent chemotherapy regimens after an initial remission were considered chemorefractory

In addition, patients were to be willing to undergo a safety follow-up for 15 years.

Test drug:

The study drug UCART19 is a frozen cell suspension of allogeneic genetically modified CD19CAR$^+$ T-cells. The drug substance is defined as allogeneic engineered CD19CAR/RQR8+_TCRαβ$^-$ T-cells. 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 (DF) of cell suspension. It was slowly administered at D0 as a single non-split dose by IV infusion over approximately 5 minutes.

Three distinct **dosage forms of UCART19** presented in the table below were manufactured.

Dosage forms of UCART19 (cells/mL)

	DF1	DF2	DF3	
			DF3.1	DF3.2
Unit dosage (CD19CAR/RQR8$^+$-TCRαβ$^-$_T-cells/mL)	6×10^5	6×10^6	1.5×10^7	2×10^7
Batch manufacturing numbers	NA	███	███	███

Four distinct **dose levels (DL) of UCART19** could be tested in this trial. The dose-escalation started at dose level 1 (DL1). A lower dose level (DL-1) could be tested in case of toxicity encountered at DL1. Patients were closely monitored for occurrence of infusion reactions. Occurrence of severe infusion reaction resulted in an immediate interruption of infusion with no possibility to resume it.

A flat UCART19 dose per patient per dose level was initially developed, with a first dose of 6×10^6 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.

To avoid the risk of a wide range of UCART19 exposure in trial patients given the variations in weight observed in the general population, and their potential impact on exposure, thus affecting DLT evaluation and interpretation, a second strategy of dosing based on 2 different weight bands had been implemented (patients weighing < 66 kg and patients weighing ≥ 66 kg). Patients ≥ 66 kg would receive a 30% higher dose than patients in the lower weight band.

As the use of partial vials was not recommended, patients enrolled at DL1 or DL-1 received a flat dose not adjusted for weight. Weight band dosing was applied for DL2 and DL3.

The table below displays the different dose levels, the corresponding flat dose per patient, the weight band dosing (number of cells and number of vials administered), and the estimated UCART19 dose/kg. The number of vials at DL2 and DL3 were adapted according to the DF of UCART19 administered (DF3.1 or DF3.2).

UCART19 dose levels

UCART19 dose level	UCART19 dose expressed in number of cells (number of vials)		Estimated UCART19 dose/kg
	Patient weight < 66 kg	Patient weight ≥ 66 kg	
DL-1	$6x10^5$ cells (1)*		$1x10^4$ cells /kg
DL1	$6x10^6$ cells (1)*		$1x10^5$ cells /kg
DL2	$6x10^7$ cells (3 to 4)	$8x10^7$ cells (4 to 6)	$1x10^6$ cells/kg
DL3	$1.8x10^8$ cells (9 to 12)	$2.4x10^8$ cells (12 to 16)	$3x10^6$ cells/kg

* for DL1 and DL-1, the weight-band strategy was not applicable as a partial vial could not be used

Comparator (Reference product and/or placebo):
Not applicable.

Non-Investigational Medicinal Product (NIMP):
Of note, these drugs were considered as IMP in Japan.
Based on previous experiences with UCART19, the lymphodepletion regimen combined fludarabine 30 mg/m^2/day IV for 3 days over 15-30 minutes from D-7 to D-5, cyclophosphamide 500 mg/m^2/day IV over 1 hour for 3 days from D-4 to D-2 and alemtuzumab IV 0.2 mg/kg/day or 8 mg/day or 12 mg/day for 5 days from D-7 to D-3. The initial dose of alemtuzumab was 0.2 mg/kg/day for 5 days (total 1 mg/kg) then a flat dose of 40 mg (8 mg/day for 5 days) (following the Amendment No. 4) tested on 3 consecutive patients could be increased to 60 mg flat dose (12 mg/day for 5 days) for all subsequent patients if the depth and duration of lymphodepletion did not allow an expansion of UCART19. Administration of alemtuzumab was at the discretion of the investigator (before Amendment N°6).

Supportive care
Antimicrobial, antifungal, and antiviral prophylaxis should be initiated at the start of lymphodepletion regimen in accordance with Institutional transplant guidelines. In addition, the surveillance/prophylaxis for opportunistic infection (viral, fungal, bacterial) was to be pursued until blood count recovery for at least 1 year post the last dose of UCART19 administration in the patients receiving alemtuzumab, during their participation in the 15-year long-term follow-up study. If indicated, IV immunoglobulins could be administered, before inclusion and throughout the study duration. Institutional guidelines for the prophylaxis and management of Tumour Lysis Syndrome (TLS) were to be followed.

Duration of treatment: single dose treatment
Screening period: 1 to 2 weeks
Lymphodepletion period: 7 days
Treatment period: 3 months
Follow-up period: 9 months

Criteria for evaluation:
Efficacy measurements:
The evaluation of the tumour load was performed on bone marrow aspirates and full blood counts.
The bone marrow cellularity, blasts cells percentage, MRD using FLC and/or qPCR were assessed during the screening period, at D-1, at D28 and along the study up to M12 or WD visit.
Response including molecular remission rate (MRD < 10^{-4} assessed by FLC and/or qPCR post treatment), morphologic complete remission rate (CR) and morphologic remission rate with incomplete blood count recovery (CRi), followed the ALL guidelines (NCCN, 2019).
Duration of remission (DoR), relapse free-survival (RFS), overall survival, progression-free survival (PFS) and proportions of patients having received an allo-HSCT were also assessed.

Safety measurements:
DLTs were assessed within 28 days after UCART19 first infusion.
The tolerance assessment of UCART19 included throughout the study:

- Record of adverse events (AEs) (including adverse events of special interest (AESI)) and toxicity; the severity of each AE was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 on a five-point scale (Grade 1 to 5), except cytokine release syndrome (CRS), TLS, acute and chronic graft *versus* host disease (GvHD) events that were graded according to the grading systems of Lee, Cairo and Harris, respectively.

- Laboratory tests: haematology, blood biochemistry and coagulation parameters. The gradable parameters were graded according to the CTCAE version 5.0.

- Vital signs (blood pressure, heart rate, respiratory rate and body temperature).

- Clinical examination including performance status (PS) according to Eastern Cooperative Oncology Group (ECOG).

- Cardiac evaluation including electrocardiogram (ECG) and left ventricular ejection fraction (LVEF).

- Neurological consultation (mandatory for France and according to local practices for other countries).

- Viral/bacterial/protozoal work-up.

BMK measurements:
BMK assessment included Interleukin (IL) 6, IL10, Tumour Necrosis Factor (TNF) α, Interferon (IFN) γ and the monitoring of the absence of RCL.

Pharmacokinetic measurements:
As this is an abbreviated report, no derived PK parameters were reported and only individual PK data (including alemtuzumab PK data) were provided.

Statistical methods:
As this was a descriptive safety and tolerability study, no formal statistical testing was performed. The statistical analyses were mainly descriptive.
In addition to data issued from the present CALM study, some data from the LTFU trial for patients previously included in CALM were considered for this clinical study report. They include the disposition of patients, allo-HSCT post-UCART19, new anti-leukemic treatment, best overall response, time-to-events endpoints (relapse, disease progression and death) and RCL.

Analysis Set:
Safety Set (SS): all patients who have received at least one course of lymphodepletion treatment and one UCART19 infusion.
DLT Evaluable Set (DLTES): all patients from the SS who were evaluable for DLT at D28 (after the first UCART9 infusion). A patient was not considered evaluable if he/she:

- Received more than 120% of the assigned dose, unless no DLT was observed.

- Received less than 80% of the assigned dose, unless a DLT was observed.

- Did not complete the safety evaluation at D28, unless a DLT was observed.

Only patients included in the escalation part were eligible for DLTES.

Study patients: disposition, baseline characteristics and follow-up
Descriptive statistics were provided for patients by dose level group and overall.
These analyses were performed using the lymphodepletion baseline (*i.e.* last reliable value prior to the start of first lymphodepletion period), and some analyses were also made at UCART19 baseline (*i.e.* last reliable value prior to the first UCART19 infusion) when indicated.

Efficacy analysis:
The following efficacy endpoints: CR rate, CRi rate, objective remission rate (ORR), MRD negative rate, best overall response (BOR), PFS, overall survival, DoR and RFS, were secondary criteria.
The proportion of patients having received an allo-HSCT was an exploratory criterion.
Efficacy analyses relatively to the first UCART19 infusion were carried out on the FAS by dose level, by LD subgroup (FC/FCA) and overall and were provided in tables. Efficacy endpoints after the second UCART19 infusion (in the framework of the study protocol or in compassionate use) were presented in listings.

Safety analysis:

The primary endpoint was the evaluation of the DLT at D28 post-first UCART19 infusion.

Descriptive statistics were provided for all safety criteria in the SS, except for DLT analysis in the DLTES, by dose level group and overall. Globally, all safety analyses were performed on the study period, except for the AESI described on the period of interest and death described on the study period and on the period of interest. Only data issued from the CALM study were considered for safety analyses, except for death. Safety data after redosing for patients retreated in compassionate use were not considered.

BMK analysis:

Descriptive statistics were provided for BMK criteria in the Biomarker Evaluable Set (BMKES).

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

A total of 25 patients were included in the CALM study. Overall, patients were followed for 9.2 months (median based on Kaplan Meier method) (range [0.72 ; 24.80] months). The disposition of patients and analysis sets are presented, overall and by dose level, in the following table. A total of 22 patients received FCA as LD regimen and 3 patients received only FC.

Disposition of included patients and analysis sets

Status		1×10^5 cells/kg (N = 6)	1×10^6 cells/kg (N = 12)	3×10^6 cells/kg (N = 7)	All (N = 25)
CALM: Included	n	6	12	7	25
in conformity with the protocol	n (%)	-	5 (41.67)	1 (14.29)	6 (24.00)
with protocol deviation(s) before or at inclusion	n (%)	6 (100)	7 (58.33)	6 (85.71)	19 (76.00)
CALM: Status of patients	n	6	12	7	25
Dose escalation phase	n (%)	6 (100)	6 (50.00)	7 (100)	19 (76.00)
Safety dose expansion phase	n (%)	-	6 (50.00)	-	6 (24.00)
Withdrawn on treatment period* due to	n	4	11	6	21
physician decision	n (%)	2 (50.00)	5 (45.45)	3 (50.00)	10 (47.62)[a]
progressive disease	n (%)	1 (25.00)	4 (36.36)	1 (16.67)	6 (28.57)
adverse event	n (%)	1 (25.00)	1 (9.09)	2 (33.33)	4 (19.05)[b]
non-medical reason	n (%)	-	1 (9.09)	-	1 (4.76)
Completed the treatment period	n	2	1		3
Withdrawn on follow-up period due to	n	-	-	1	1
death	n (%)	-	-	1 (100)	1 (100)
LTFU: Included	n (%)	4 (66.67)	9 (75.00)	4 (57.14)	17 (68.00)
LTFU: Status of patients	n	4	9	4	17
Withdrawn due to	n	3	3	2	8
death	n (%)	-	2 (66.67)	1 (50.00)	3 (37.50)
progressive disease	n (%)	2 (66.67)	-	-	2 (25.00)
adverse event	n (%)	1 (33.33)	1 (33.33)	-	2 (25.00)
other	n (%)	-	-	1 (50.00)	1 (12.50)
Ongoing patients**	n	1	6	2	9
CALM study sets					
Included Set	n	6	12	7	25
Safety Set	n (%)[c]	6 (100)	12 (100)	7 (100)	25 (100)
Full Analysis Set	n (%)[c]	6 (100)	12 (100)	7 (100)	25 (100)
DLT Evaluable Set	n (%)[d]	6 (100)	6 (50.0)	6 (85.7)	18 (72.0)
Biomarker Evaluable Set	n (%)[d]	6 (100)	12 (100.0)	7 (100)	25 (100)
LTFU study set					
Included Set (LTFU)	n	4	9	4	17

Percentages are based on n

Follow-up period of the CALM study is only applicable for patients included after amendment 4 (from the patient 022)

* The study treatment period is defined as per protocol

** Data cut-off = 22 October 2020 (i.e. database lock of the CALM study)

[a] *including 7 patients for allo-HSCT.*

[b] *multiple organ dysfunction syndrome and sepsis; malignant neoplasm progression; pulmonary haemorrhage; multiple organ dysfunction syndrome and neutropenic sepsis.*

[c] *% based on the Included Set.*

[d] *% based on the Safety Set.*

BASELINE CHARACTERISTICS

Overall, the patients included in the CALM study were aged 18.0 to 64.0 years with a median of 37.0 years and most of them (80.0%) were between]18-55] years. Of note, in the UCART19 $1x10^5$ cells/kg group, patients were younger (median = 22.5 years) than in the other dose level groups (median = 40.0 years in the UCART19 $1x10^6$ cells/kg group and 39.0 years in the UCART19 $3x10^6$ cells/kg group). More than half of the patients were male (56.0%) and most were White (68.0%). Among the 23 patients with a value at baseline, all except one had ECOG PS equal to 0 or 1 (value = 2 in one patient).

According to the WHO classification, 4 patients (16.0%) were diagnosed with B-ALL with t(9;22) (q34;q11.2), one patient (4.0%) with B-ALL with hyperdiploidy, one patient (4.0%) with B-ALL with hypodiploidy, one patient (4.0%) with B-ALL with t(12;21)(p13;q22), one patient (4.0%) with B-ALL with t(1;19)(q23;p13.3), one patient (4.0%) with B-ALL with t(v;11q23) and 16 patients (64.0%) were diagnosed with B-ALL not otherwise specified. The median disease duration since diagnosis was 2.3 years (range [0.10 ; 7.50] years). At study entry, 16 patients (64.0%) had been refractory to previous treatment for 1.2 months in median (range [0.03 ; 40.01] months) and 9 (36.0%) in relapse for 1.3 months in median (range [0.66; 3.12] months). At baseline, prior to the first lymphodepletion, 3 patients (12.0%) had a bone marrow blasts value < 5%, 7 patients (28.0%) a value in the range [5-25]%, 5 patients (20.0%) a value in the range]25-50]% and 10 patients (40.0%) a value > 50%. Among the patients with a value at baseline, prior to the first lymphodepletion, all had a minimal residual disease > 10^{-3} assessed by qPCR and/or FLC.

All patients received drug treatment as previous therapy, 72.0% underwent a previous allo-graft, and 48% a previous radiotherapy. Combination of therapies included combination of drug treatment with: either allo-graft + radiotherapy (40.0%), allo-graft (32.0%), or radiotherapy (8.0%), and combination of only drugs in 20.0%. Patients received from 1 to 6 drug treatment lines with a median of 4.0 lines and 64.0% received at least 4 drug treatment lines. As planned in the protocol, if deemed necessary by the investigator, a cytoreductive chemotherapy was administered before initiation of the lymphodepletion regimen in 52.0%.

This Phase I study was conducted in patients with relapsed or refractory CD19 positive B-ALL, for which baseline characteristics were broadly in accordance with the target population defined in the study protocol.

EXTENT OF EXPOSURE

For the first UCART19 infusion, all patients except 2 patients had a relative volume administered of UCART19 equal to 100% of the intended volume (values for the 2 other patients: 75.0% and 93.8%, respectively, reported as protocol deviations).

Three patients (one patient in the UCART19 $1x10^6$ cells/kg group and 2 in the UCART19 $3x10^6$ cells/kg group) received a second UCART19 infusion in the framework of the CALM study, with a relative volume administered of 100%.

In addition, 2 patients (one patient in the UCART19 $1x10^5$ cells/kg group and the other in the UCART19 $1x10^6$ cells/kg group) had re-dosing with UCART19 in compassionate use.

EFFICACY RESULTS

Secondary endpoints

Among the 25 patients of the FAS, 12 (48.0%) were considered as responders post-first UCART19 infusion, with as **best overall response**: MRD negative CRi in 7 patients (28.0%), MRD negative CR in 2 patients (8.0%), morphologic CRi in 2 patients (8.0%) and MRD indeterminate CR in one patient (4.0%).

Twelve patients (48.0%) were non-responders with as BOR: refractory disease in 6 patients (24.0%), relapse disease and progressive disease in 3 patients (12.0%), each.

One patient was non-evaluable.

Thus, according to BOR post-first UCART19 infusion, the **objective response rate** was 48.0% (12 patients, 95% CI [27.80;68.69]) with 36.0% for CRi rate (9 patients, 95% CI [17.97;57.48]) and 12.0% for CR rate (3 patients, 95% CI [2.55;31.22]).

Among the 12 patients with an objective remission, the MRD negative rate was 75.0% (9 patients, 95% CI [42.81;94.51]).

Regarding the 3 patients with redosing in the framework of the CALM study, all had refractory disease as BOR post-first UCART19 infusion. One patient remained with refractory disease as BOR post-second UCART19 infusion, one was non-evaluable and the third had a MRD negative CRi.

Concerning the 2 patients with redosing in compassionate use, one patient had MRD negative CRi as BOR post-first UCART19 infusion and MRD indeterminate CRi as BOR post-second UCART19 infusion and the other patient with progressive disease in post-first UCART19 infusion was not evaluable in post-second UCART19 infusion.

Considering all patients of the FAS, the median of the **progression free survival** post-first UCART19 infusion was estimated at 2.1 months (95% CI [1.2;2.8]) with analysis ignoring allo-HSCT and 1.6 months (95% CI [1.0;2.8]) with analysis censoring at the time of allo-HSCT.

The median of the **overall survival** was estimated at 13.4 months (95% CI [4.8;23.0]). The survival rate at 6 months was 61% (95% CI [38%;77%]).

Among the 12 responder patients post-first UCART19 infusion, the median of the **relapse free survival** was estimated at 7.4 months (95% CI [1.8;.] with analysis ignoring allo-HSCT and 1.8 months (95% CI [1.5;.]) with analysis censoring at the time of allo-HSCT.
Relapse free survival rates at 3 months and 6 months were both 55% (95% CI [23%;78%]) (analysis ignoring allo-HSCT).

Among the 12 responder patients post-first UCART19 infusion, the median of the **duration of remission** was estimated at 7.4 months (95% CI [1.8;.] with analysis ignoring allo-HSCT and 1.8 months (95% CI [1.5;.]) with analysis censoring at the time of allo-HSCT.

Exploratory endpoints:
A total of 9 patients (36.0%) received one **allo-HSCT** post-first UCART19 infusion, considering only patients grafted before new anti-leukemic treatment or second infusion.

Regarding patients with redosing, one patient out of the 3 receiving a second UCART19 infusion in the framework of the CALM study and both patients with redosing in compassionate use received an allo-HSCT after the second infusion.

SAFETY RESULTS

- **Dose Limiting Toxicities**
During the dose escalation phase, among the 18 patients evaluable for DLTs, 3 patients (16.7%) experienced DLT, *i.e.* one patient in each of the 3 groups. The patient in the UCART19 $1x10^5$ cells/kg group presented CRS grade ≥ 4 and the other 2 patients encountered another unacceptable toxicity, in view of the investigator and the DSMB, *i.e.* prolonged cytopenia grade 4.

Following mTPI recommendation, the MTD (*i.e.* the highest dose at which the toxicity probability is the closest to the target probability of 0.3) was defined as the DL3 ($3x10^6$ cells/kg). According to DSMB meeting conclusion, the RD was defined as the DL2 ($1x10^6$ 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. Then, as planned in the clinical study protocol, 6 additional patients were treated at this RD in the expansion part.

- **Emergent adverse events**
The following table summarises the main results of adverse events during the study period, in the Safety Set.

Overall summary for adverse events during the study period in the Safety Set					
		$1x10^5$ cells/kg	$1x10^6$ cells/kg	$3x10^6$ cells/kg	**All**
CALM study	N	6	12	7	25
Patients having reported (during the study period) at least one:					
EAE	n (%)	6 (100)	12 (100)	7 (100)	25 (100)
EAE related to at least UCART19	n (%)	6 (100)	10 (83.3)	7 (100)	23 (92.0)
Severe EAE (grade ≥ 3)	n (%)	6 (100)	10 (83.3)	7 (100)	23 (92.0)
Severe EAE (grade ≥ 3) related to at least UCART19	n (%)	4 (66.7)	3 (25.0)	4 (57.1)	11 (44.0)
Serious AE (including death)	n (%)	6 (100)	6 (50.0)	7 (100)	19 (76.0)
Serious EAE (including death)	n (%)	6 (100)	6 (50.0)	7 (100)	19 (76.0)
Serious EAE related to at least UCART19	n (%)	3 (50.0)	4 (33.3)	5 (71.4)	12 (48.0)
Patients who died (during CALM study)	n (%)	2 (33.3)*	2 (16.7)	3 (42.9)	7 (28.0)
LTFU study	N	4	9	4	17
Patients who died (during LTFU study)	n	3	3	1	7

Study period lymphodepletion period + treatment period + follow-up period
* In addition, one patient reported an emergent fatal AE during the first follow-up period but leading to death during the LTFU study.

Of note, emergent adverse events (EAE) were described hereafter considering overall UCART19 groups, as the number of patients in each group was low. Therefore, although few differences could be detected in term of frequency across the UCART19 dose level groups, no comparison could be done.

All patients of the Safety Set reported at least one EAE during the study period. The ***most frequently affected SOCs*** (≥ 60% of patients overall) during the study period were Immune system disorders (88.0% of patients), Gastrointestinal disorders (76.0%), Infections and infestations (72.0%), Investigations (72.0%), Blood and lymphatic system disorders (68.0%) and General disorders and administration site conditions (64.0%).

The ***most commonly reported EAEs*** (≥ 20% of patients overall) during the study period were CRS (88.0% of patients), anaemia (56.0%), infusion-related reaction (52.0%), nausea (44.0%), pyrexia (40.0%), thrombocytopenia (32.0%), febrile neutropenia, headache (28.0% each), cytomegalovirus (CMV) infection reactivation, diarrhoea, neutropenia (24.0% each), abdominal pain, back pain, blood bilirubin increased, cytopenia (corresponding to Lowest Level Term Prolonged cytopenia as per protocol definition) and platelet count decreased (20.0% each).

Most of the patients (92.0%) reported at least one severe EAE (CTCAE grade ≥ 3). The ***most commonly reported severe EAEs*** (≥ 15% of patients overall) during the study period were anaemia (56.0% of patients with EAEs rated grade 3), thrombocytopenia (32.0% of patients, including 8.0% of patients with EAEs rated grade 3 and 24.0% grade 4), febrile neutropenia (28.0%: 24.0% grade 3 and 4.0% grade 4), neutropenia (24.0%: 4.0% grade 3 and 20.0% grade 4), prolonged cytopenia (20.0% of patients with EAEs rated grade 4), platelet count decreased (20.0%: 12.0% grade 3 and 8.0% grade 4), neutrophil count decreased (16.0% of patients with EAEs rated grade 4) and CRS (16.0%: 12.0% grade 3 and 4.0% grade 4).

Most of the patients (92.0%) reported at least one EAE considered to be related to at least UCART19. The ***most commonly reported EAEs related to at least UCART19*** (≥ 15% of patients overall) during the study period were CRS (88.0% of patients), headache and neurotoxicity (16.0% each).

Overall, 44.0% of patients had at least one severe EAE related to at least UCART19. The ***most commonly reported severe EAEs related to at least UCART19*** (≥ 10% of patients overall) during the study period were CRS (16.0%), anaemia, thrombocytopenia, prolonged cytopenia, bone marrow failure and hemophagocytic lymphohistiocytosis (12.0%, each).

A total of 19 patients (76.0%) experienced at least one serious emergent adverse event (SEAE) including death during the study period. ***The most commonly reported SEAEs*** (≥ 10% of patients overall) were CRS (40.0%), febrile neutropenia (28.0%), prolonged cytopenia (20.0%), adenovirus infection, CMV infection reactivation, lower respiratory tract infection fungal, hemophagocytic lymphohistiocytosis, bone marrow failure, neutropenia, thrombocytopenia, lymphocyte count decreased and multiple organ dysfunction failure (12.0% each).

Overall, 12 patients (48.0%) reported at least one SEAE related to at least UCART19 during the study period. ***The most commonly reported SEAEs related to at least UCART19*** (≥ 10% of patients overall) were CRS (40.0%), bone marrow failure, prolonged cytopenia and hemophagocytic lymphohistiocytosis (12.0% each).

A total of ***7 patients (28.0%) died during the CALM study*** (3 patients during the first post-UCART19 period, 3 during the first FU period and one during the second FU period):

- 2 patients (33.3%) in the UCART19 $1x10^5$ cells/kg group:
  • Multiple organ dysfunction syndrome and neutropenic sepsis, both considered related to UCART19 and to lymphodepletion, during the first post-UCART19 period.
  • Respiratory tract infection, during the first FU period, not considered as related to UCART or to lymphodepletion.

- 2 patients (16.7%) in the UCART19 $1x10^6$ cells/kg group:
  • Septic shock, during the first post-UCART19 period, considered as related only to the lymphodepletion.
  • Pulmonary haemorrhage occurring in a context of disseminated adenovirus, considered related only to UCART19, during the first FU period in post allo-HSCT setting.

- 3 patients (42.9%) in the UCART19 $3x10^6$ cells/kg group:
  • Multiple organ dysfunction syndrome and sepsis, both considered related to UCART19 and to lymphodepletion, during the first FU period in post allo-HSCT setting.
  • Malignant neoplasm progression, during the first post-UCART19 period, not considered as related to UCART19 or lymphodepletion.
  • Central nervous system leukaemia, during the second FU period, not considered as related to UCART19 or lymphodepletion.

In addition, ***7 patients died during the LTFU study***: 3 patients in the UCART19 $1x10^5$ cells/kg group (leukemic infiltration extramedullary, acute lymphocytic leukaemia and multiple organ dysfunction syndrome), 3 patients in the UCART19 $1x10^6$ cells/kg group (acute lymphocytic leukaemia recurrent, neutropenic sepsis and acute lymphocytic leukaemia recurrent and aspergillus infection) and one patient in the UCART19 $3x10^6$ cells/kg group (central nervous system leukaemia).

Remark: A total of 8 patients (32.0%) presented at least one ***emergent fatal AE on CALM study period***, *i.e.* the 7 patients who died during the CALM study (described above) plus one patient in the UCART19 $1x10^5$ cells/kg group reporting an emergent fatal AE, multiple organ dysfunction syndrome, during the first follow-up period but leading to death during the LTFU study.

- **AE of special interest**
During the first post-UCART19 period
Regarding *cytokine release syndrome*, a total of 20 (80.0%) out of 25 patients treated with UCART19 experienced 20 CRS (all related to at least UCART19, 4 severe events in 4 patients [3 events grade 3 and one grade 4] and 9 serious events in 9 patients) and 3 hemophagocytic lymphohistiocytosis (all severe [2 events grade 3 and one grade 4], serious and related to at least UCART19).

A total of 3 patients (12.0%) (all in the UCART19 $1x10^5$ cells/kg group) reported 4 *immediate infusion-related reaction other than CRS*. None of these events were severe or serious and none was considered to be related to at least UCART19.

Two cases of *tumour lysis syndrome* occurred in 2 patients (8.0%), both were severe (grade 3) and serious. One case was related to at least UCART19.

Two cases of *acute graft versus host disease in skin* grade 1 occurred in 2 patients (8.0%), one was serious. Both were related to at least UCART19.

A total of 14 patients (56.0%) experienced 33 *neurological events*. The main events reported (≥ 15.0% of patients overall) were headache (20.0%) and neurotoxicity (16.0%). Six events in 3 patients (12.0% of patients) were rated severe (2 grade 3 and 4 grade 4) and 11 events in 3 patients (12.0%) were serious. A total of 7 patients (28.0%) had 19 neurological events considered to be related to at least UCART19, all rated grade 1 except 4 events rated grade 4.

Regarding *B cell aplasia and resultant hypogammaglobulinemia*, a total of 5 patients (20.0%) experienced 4 prolonged cytopenia (all severe [grade 4], serious and 2 events related to at least UCART19) and 3 hypogammaglobulinemia (all related to at least UCART19, none severe and one serious event).

A total of 17 patients (68.0%) experienced 34 events of *infection*. The main event reported ($\geq$ 15.0% of patients overall) was CMV infection reactivation (20.0%). Fourteen events in 9 patients (36.0% of patients) were rated severe (9 grade 3, 3 grade 4 and 2 grade 5) and 19 events in 10 patients (40.0%) were serious. Infections related to lymphodepletion and/or UCART19 during the first post-UCART19 period occurred in 12 patients (48.0%) (25 events). A total of 5 patients (20.0%) had 6 events of infection considered to be related to at least UCART19 including 1 event grade 3, 1 grade 4 and 1 grade 5. Two patients died from neutropenic sepsis and septic shock, respectively, during the first post-UCART19 period, as already described previously.

During the second post-UCART19 period
Both patients in the UCART19 $3x10^6$ cells/kg group receiving a second UCART19 infusion in the framework of the CALM study suffered from *cytokine release syndrome*, during the second post-UCART19 infusion. Both events were considered as related to at least UCART19. None was severe and one was serious.

The patient in the UCART19 $1x10^6$ cells/kg group receiving a second UCART19 infusion in the framework of the CALM study reported one non-severe event of headache as *neurological event*. This event was neither serious nor considered to be related to at least UCART19.

Both patients receiving a second UCART19 infusion in the UCART19 $3x10^6$ cells/kg group suffered from 3 events of *infection*: 1 serious event, no severe event and no event related to at least UCART19.

During the first FU period
Regarding *new malignancy*, one serious event of acute lymphocytic leukaemia recurrent was reported in one patient in the UCART19 $3x10^6$ cells/kg group, this event was not severe and not considered to be related to at least UCART19.

A total of 4 patients (30.8%) experienced 4 events of *new hematologic disorder* : 1 severe (grade 4) and serious event of platelet count decreased, 1 severe (grade 3) and serious event of febrile neutropenia, 1 severe (grade 3) event of thrombocytopenia and 1 non-severe and serious event of acute lymphocytic leukaemia recurrent (event already described above). None of these events were related to at least UCART19.

One patient in the UCART19 $1x10^5$ cells/kg group presented disorientation and hallucination as *incidence/exacerbation of neurologic disorder*. These 2 events were neither severe nor serious nor related to at least UCART19.

During the second FU period
Regarding *new malignancy*, one patient among the 2 receiving a second UCART19 infusion in the UCART19 $3x10^6$ cells/kg group presented 2 serious events: leukemic infiltration extramedullary (non-severe) and central nervous system leukaemia (severe, fatal). None was related to at least UCART19.

This same patient presented 6 events of *new hematologic disorder*: prolonged cytopenia, neutropenia, thrombocytopenia (all severe [grade 4], serious and considered as related to at least UCART19), lymphadenopathy (non-severe, non-serious and not considered as related to at least UCART19), central nervous system leukaemia and leukemic infiltration extramedullary (both events described above).

Regarding *B cell aplasia and resultant hypogammaglobulinemia*, the same patient reported one event of prolonged cytopenia, already described above.

During the first period (first post-UCART19 and first FU periods)
Regarding *prolonged cytopenia*, a total of 4 patients (16.0%) suffered from prolonged cytopenia, all severe (grade 4) and serious and 2 considered as related to at least UCART19, already described previously during the first post-UCART19 period.

During the second period (second post-UCART19 and second FU periods)
Regarding *prolonged cytopenia*, one patient in the UCART19 $3x10^6$ cells/kg group reported one event of prolonged cytopenia, already described previously during the second FU period.

- **Laboratory tests**

For *blood biochemical parameters* rated according to the CTCAE version 5.0 grading, emergent severe (grade 3 or 4) abnormal values were sparsely distributed among biochemical parameters. The most frequent emergent severe abnormal values (reported in at least 2 patients overall) on study period were high gamma-glutamyl transferase (3 patients, 13.6%), high aspartate aminotransferase (2 patients, 8.3%), high creatinine (2 patients, 8.0%) and hypomagnesemia (2 patients, 8.0%). All emergent severe abnormal values were rated grade 3 except for hypomagnesemia rated grade 4 in both patients.

For *blood haematological parameters* rated according to the CTCAE version 5.0 grading, emergent severe abnormal values were detected for low lymphocytes (88.0% of patients, grade 4), low neutrophils (80.0%, including 12.0% of patients with values rated grade 3 and 68.0% grade 4), low white blood cells (68.0%, grade 4), low platelets (62.5%, including 20.8% of patients with values rated grade 3 and 41.7% grade 4) and anaemia (60.0%, grade 3).

For *coagulation parameters* rated according to the CTCAE version 5.0 grading, emergent severe abnormal values were detected for low fibrinogen (8.7% of patients, all grade 4).

- **Other safety evaluation**

Vital signs, clinical examination and ECOG performance status
Overall, no clinically relevant median change over time considering the last post-baseline value was observed except for the weight (-1.6 kg).

Regarding *ECOG performance status,* a total of 17 patients (68.0%) had a worsening from baseline to post-baseline, considering the worst (highest) post-baseline value: 6 patients (24.0%) (from 0 to 1), 4 patients (16.0%) (from 0 to 2), 4 patients (16.0%) (from 1 to 2), 1 patient (4.0%) (from 1 to 3) and 2 patients (8.0%) (from 1 to 4). In addition, 2 patients (8.0%) with a missing value at baseline had ECOG PS = 1 at post-baseline.

Electrocardiogram
One patient in the UCART19 1×10^6 cells/kg group had at least one ECG abnormality considered as clinically significant by the investigator.

Left Ventricular Ejection Fraction
At baseline, among the 24 patients assessable, 23 patients (95.8%) had an LVEF $\geq$ 50% and one patient had a value in the range [40-50% [. At the end of study (n = 10 assessable patients), all had an LVEF $\geq$ 50%. No patient (n = 9 assessable patients) had LVEF decrease from baseline greater than 10%.

Infections
A total of 10 patients (40.0%) had clinically significant viral abnormalities and 2 patients (9.1%) had clinically significant bacterial abnormalities, during the study period.

BMK RESULTS:
In the BMKES, the concentrations of main **circulating proteins** (IL6, IL10, TNFα and IFNγ) measured by multiplex Meso Scale Discovery (MSD) immunoassay were in the assay range at each visit except for IL10 at UCART19 baseline (one patient with a value < Lower Limit of Quantification (LLOQ)) and for IFNγ at D021 (one patient with a value < LLOQ). Patients with severe CRS ($\geq$ grade 3) tended to show higher peaks of IL10 and IFNγ than patients with CRS grade [0-2]. Results should however be interpreted with caution due to the limited number of patients with a severe CRS (n = 3) among the assessable patients.
No **replication competent lentivirus** was detected in tested patients by vesicular stomatitis virus G glycoprotein qPCR at each visit.

CONCLUSION

This international, multicentre, open-label, dose-escalating, first in human CALM study was conducted in 25 adults with relapsed or refractory CD19 positive B-ALL to assess the safety and tolerability of ascending doses of UCART19, given as a single infusion (with the possibility of re-dosing).

According to best overall response post-first UCART19 infusion, the objective response rate (complete remission or complete remission with incomplete blood count recovery) was 48.0% (95% CI [27.80;68.69]) *i.e.* 12 responder patients. In these patients, the MRD negative rate was 75.0% (95% CI [42.81;94.51]) and the median of the duration of remission according to analyses ignoring allo-HSCT or censoring at the time of allo-HSCT was estimated at 7.4 months (95% CI [1.8;.]) and 1.8 months (95% CI [1.5;.]), respectively.

Considering all patients, the median of the progression free survival post-first UCART19 infusion was estimated at 2.1 months (95% CI [1.2;2.8]); analysis ignoring allo-HSCT) and 1.6 months (95% CI [1.0;2.8]); analysis censoring at the time of allo-HSCT).

During the dose escalation phase, 3 patients out of 18 evaluable patients (one patient in each of the 3 dose level groups) experienced DLT. Following mTPI recommendation, the MTD was defined as the UCART19 DL3 ($3x10^6$ cells/kg) and according to DSMB meeting conclusion, the recommended dose was defined as the UCART19 DL2 ($1x10^6$ cells/kg).

All patients reported at least one EAE during the study period. Most of the patients (92.0%) reported at least one EAE considered to be related to at least UCART19, mainly cytokine release syndrome (88.0% of patients), headache and neurotoxicity (16.0% each). Overall, 92.0% of patients reported at least one severe EAE (grade ≥ 3 according to CTCAE), mainly anaemia (56.0% of patients), thrombocytopenia (32.0%) and febrile neutropenia (28.0%). A total of 19 patients (76.0%) experienced at least one SEAE including death, mainly cytokine release syndrome (40.0% of patients), febrile neutropenia (28.0%) and prolonged cytopenia (20.0%).

The Sponsor reviewed its development strategy and decided to stop the development of UCART19 in the indication of relapsed /refractory B-ALL. This decision was not due to safety concerns. This study has been completed.

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Version of the report: Final version