2. SYNOPSIS

<table>
<tr><td colspan="2">Name of sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex – France
Local sponsors:
Servier Research & Development Ltd, Sefton House, Sefton Park, Bell Hill, Stoke Poges, Slough, Berkshire, SL2 4JS - United Kingdom
Laboratorios Servier, S.L., Avenida de los Madroños, 33 - CP 28043 Madrid - Spain</td><td>(For National Authority Use only)</td></tr>
<tr><td colspan="2">Test drug
Name of Finished Product:
Not applicable
Name of Active Ingredient:
Universal Chimeric Antigen Receptor T-cells targeting CD19 (UCART19) (S68587): CD19CAR/RQR8^{+}_TCRαβ^{-}_T-cells</td><td></td></tr>
<tr><td>Individual Study Table Referring to Part of the Dossier</td><td>Volume:</td><td>Page:</td></tr>
<tr><td colspan="3">Title of study: A phase I, 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.
UCART19-PALL study (UCART19 in Paediatric Acute Lymphoblastic Leukaemia).
Protocol No.: CL1-68587-001 (UCART19_02)
EudraCT No.: 2015-004293-15
The description of the study protocol given hereafter includes the modifications of the 7 substantial amendments to the protocol applicable in all countries.</td></tr>
<tr><td colspan="3">Main Investigator
Not applicable</td></tr>
<tr><td colspan="3">Study countries:
In all, 4 centres in 3 countries included 13 patients:
- 6 patients in the United Kingdom (1 centre).
- 5 patients in the United States (2 centres).
- 2 patients in France (1 centre).
Of note, the third centre planned in the United States and the centre planned in Spain did not include any patient. One centre in Belgium was opened and was closed before the end of the study without having selected or included patient.</td></tr>
<tr><td colspan="3">Publication (reference):
Not applicable</td></tr>
<tr><td colspan="2">Studied period:
Initiation date (first visit first patient): 03 June 2016
Last visit last patient date: 17 September 2020
Completion date (date of the discontinuation of the study following the sponsor’s decision): 04 November 2020
[redacted] This decision was not due to safety concerns. Therefore, the present clinical study report (CSR) is abbreviated.</td><td>Phase of development of the study:
Phase I</td></tr>
<tr><td colspan="3">Objectives:
Primary objective
- To evaluate the safety of UCART19 in paediatric patients with relapsed /refractory B-cell acute lymphoblastic leukaemia (R/R B-ALL).
Secondary objective
- To determine the ability of UCART19 to achieve molecular remission at Day (D) 28 after the first UCART19 infusion.</td></tr>
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Exploratory objectives

- To determine the ability of UCART19 to achieve molecular remission at D56, D84, Month (M) 4, M6, M9 and M12 after the first UCART19 infusion.
- To assess the remission rate, duration of remission (DoR), time to remission, overall survival (OS), and progression free survival (PFS) after the first UCART19 infusion.
- To assess the proportion of patients who underwent a re-dosing with UCART19.
- To assess the proportion of patients who underwent allogeneic-Hematopoietic Stem Cell Transplantation (allo-HSCT) following UCART19 infusion.
- To analyse the expansion, phenotype, trafficking and persistence of UCART19 by assessing the cellular kinetic profile of UCART19 and by characterizing various UCART19 cell subsets at different time-points.
- To assess cytokine release and C-reactive protein levels.
- To investigate the potential development of an anti-UCART19 immune response.
- To monitor the immune cell depletion and reconstitution resulting from the lymphodepletion (LD) and UCART19 treatments by assessing the kinetics of host peripheral B-cell, T-cell, and Natural Killer cell subsets.
- To assess the potential switch of CD19 expression on patient's leukaemia cells.
- To assess CD52 expression data on patient's leukaemic cells.
- To monitor the absence of Replication Competent Lentivirus (RCL).
- To perform a retrospective genomic analysis, in case a T-cell transformation was observed.

Methodology:
This was a phase I, open-label, non-comparative, first-in-human study in paediatric patients with R/R CD19-positive B-ALL.

The progress of the study was driven by the Data Safety Monitoring Board (DSMB) who reviewed the safety data in the light of efficacy data every three patients after they had reached a period of treatment of 28 days post-infusion. During these meetings, all data from the previous group(s) and data from the current group were assessed as an aggregate data set, in order to give recommendations on further enrolments for the next group. Within the first group of 3 patients, the full safety data of each patient treated were reviewed by the DSMB after 28 days post infusion, and the next patient was enrolled as per the DSMB recommendations. Within the following groups, the patients were treated respecting a minimum interval of 2 weeks before the dosing of each subsequent patient. However, in case of occurrence of any major toxicity (pre-established criteria), the dosing of the subsequent patient was postponed until the meeting of the DSMB at the end of the 28 days following UCART19 infusion of the previous patient. Following this safety review, the next patients could be enrolled upon recommendations of the DSMB.
From the 10th patient enrolled, the enrollment strategy was revised:

- In case no pre-established criteria for toxicity were encountered, the parallel enrolment was set-up, after validation by DSMB members.
- If pre-established criteria for toxicity were encountered, the enrolment strategy remained the same as previously described.

The study was divided into the following periods for each patient:
Screening period/Inclusion
After signature of the general Patient Information Sheet and Informed Consent Form, patients were to enter a screening period (within 1 or 2 weeks) during which the eligibility criteria were to be checked and bone marrow (BM) was to be assessed. Before entering in the study protocol and according to their tumour burden and the investigator's judgment, patients could receive a dexamethasone-based cytoreductive chemotherapy as part of the routine care during approximately a 7-day period (not a requirement of the protocol) that had to be completed before the initiation of lymphodepletion at D-4 (D-7 before Amendment N°9).

Lymphodepletion treatment period: from D-4 to D-1 prior to UCART19 infusion
The LD treatment was to start as early as possible after the inclusion (within 3 days if possible) and after the patient had completed the cytoreduction treatment if applicable. Following Amendment N°9, the LD period was reduced from 7 days (from D-7 to D-1) to 4 days (from D-4 to D-1). A fludarabine/cyclophosphamide/alemtuzumab (FCA) regimen was administered during this period. Before Amendment N°9, alemtuzumab was not mandatory.

The patient could be hospitalized, according to the local practices per country, from 4 days before the administration of UCART19 (D-4) (D-7 before Amendment N°9) or the day before the administration of UCART19 (D-1) to closely manage the toxicities during the LD.
At the end of the LD treatment period, eligibility criteria allowing UCART19 administration were to be assessed within 24 hours prior to infusion in order to ensure patients' safety and a bone marrow aspirate (BMA) was to be performed on the day preceding UCART19 administration (D-1), in order to check the tumour burden in the marrow as close as possible to UCART19 infusion.

Treatment Period: from D0 (UCART19 infusion) to D84 post-UCART19 infusion
Status of infection had to be evaluated before UCART19 dosing. If patient did not qualify for UCART19 infusion after the start of LD, UCART19 dosing could be delayed for up to 21 days following the last day of the LD treatment. On D0, patients received a single intravenous (IV) dose of UCART19.
For each patient, safety assessments were to be performed at D28 post UCART19 administration.
Safety stopping rules were to be discussed with the DSMB.

Follow-up (FU) Period: from D85 to M12
Patients were closely monitored during this 9-month FU period at a hospital/ambulatory care unit after D84 until M12.

End of study (EOS)/Withdrawal (WD) visit
At M12 (EOS visit) or WD visit, a complete evaluation was to be conducted according to the investigations schedule.
After completion of EOS/WD visit, patients were to participate in a separate Long-Term Follow-Up (LTFU) study (under a separate protocol) and were to be followed for 15 years. Consent for the LTFU study was planned to be taken as soon as appropriate after the start of the PALL study and if possible within the first 3 months after UCART19 infusion.

The reasons for premature end of study participation were:

- Adverse events incompatible with the administration of the Investigational Medicinal Product according to the judgment of the investigator.
- Pregnancy.
- Non-medical reason (to be carefully described) *e.g.* consent withdrawal.
- Bone marrow transplantation: patient had to withdraw the day before the initiation of the conditioning regimen. This criteria for withdrawal was added in the Amendment N°4.
- Availability of a therapeutic alternative for the patient as per physician's decision (*e.g.* anti-leukaemic treatment); the patient had to withdraw the day before the initiation of the anti-leukaemic treatment.

From the moment the patient was withdrawn from the PALL study, he/she was to immediately transition into the LTFU study.

UCART19 re-dosing (optional)
From 14 days (28 days before Amendment N°9) to 9 months after the first UCART19 infusion, a patient could be considered for re-dosing with UCART19, according to the criteria for re-administration defined in the study protocol. The overall safety of the patient was to be assessed and reviewed between the investigators, the sponsor and DSMB members before making the decision to re-dose the patient. The patient eligible for re-dosing then started a new treatment cycle from D-4 (D-7 before Amendment N°9) until D84 and followed the same schedule of visits and assessments as described for the initial UCART19 infusion.
A cytoreductive chemotherapy could be administered before initiation of the LD regimen at D-4 (D-7 before Amendment N°9), if deemed necessary by the investigator. The same LD regimen as the last LD treatment received could be applied or the regimen could be adapted (in terms of combination of drugs and/or of doses of each drug, following discussions with the sponsor).
After completing a 3-month period after the last UCART19 infusion, the patient switched to the FU period, starting at the next scheduled visit in the study plan, calculated from the first UCART19 infusion (*i.e.* initial D0) up to the end of 3-month period after the last UCART19 infusion.
Re-dosing could not occur after 9 months following initial D0 (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.

Number of patients:
Planned: 18 patients maximum
Included: 13 patients

Diagnosis and main criteria for inclusion:

Patients were 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% leukaemic blasts in the BM.
- Or presenting a quantifiable Minimal Residual Disease (MRD) load of ≥ $1x10^{-3}$ (by multiparameter flow cytometry [FLC] and/or quantitative polymerase chain reaction [qPCR]) at the end of the last induction treatment.
- Who had exhausted alternative treatment options.

Relapsed disease is defined as:

- Second or subsequent BM relapse.
- Or any BM relapse after allo-Stem Cell Transplantation.

Refractory disease is defined by not achieving an initial complete response after 2 cycles of a standard chemotherapy regimen (primary refractory). Subjects who were refractory to subsequent chemotherapy regimens after an initial remission were considered chemo-refractory.

In addition, patients were to be willing to undergo a safety FU for 15 years.

Investigational Medicinal Product:
UCART19 is a frozen suspension of allogeneic genetically modified T-cells expressing a CD19 CAR, cryopreserved in an infusible grade cryomedium. The drug substance of UCART19 is defined as allogeneic engineered CD19CAR/RQR8^{+}_TCRαβ^{-}_T-cells. It is supplied as a suspension for intravenous infusion conditioned in 1.8 mL cryovials containing approximately 1 mL of a given dosage form of cell suspension. 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 $3x10^{6}$ CD19CAR/RQR8^{+}_TCRαβ^{-}_T-cells /kg. The number of vials to use per patient was dependent upon the patient actual weight at the time of infusion and upon the dosage form used.
The patients were closely monitored for occurrence of infusion reactions during the infusion. Occurrence of a severe infusion reaction necessitated an immediate interruption of the infusion with no possibility to resume it.

Batch manufacturing numbers: [redacted]

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

Non Investigational Medicinal Product:
Based on previous experiences with UCART19, the LD regimen started from D-7 (or D-4 according to Amendment No.9) and, depending on the Amendment, combined fludarabine 30 mg/m^2/day IV over 15/30 minutes for 3 to 5 days, cyclophosphamide with doses from 500 mg/m^2/day for 3 days or 800 mg/m^2/day for 2 days and up to 60 mg/kg/day for 2 days, with or without alemtuzumab 1 mg/kg total dose administered over 3 to 5 days (capped at 40 mg total dose from Amendment No.6). Depending on the patient's status, this LD regimen could be adapted upon agreement from the sponsor, the DSMB, and the investigator.

Supportive care:
Institutional transplant guidelines for antimicrobial, antifungal, and antiviral prophylaxis for opportunistic infections were to be followed. In addition, the surveillance/prophylaxis for opportunistic infection (viral, fungal, bacterial) were to be pursued until blood count recovery in those subjects receiving alemtuzumab.
Institutional guidelines for the prophylaxis and management of tumour lysis syndrome (TLS) were to be followed. Tocilizumab had to be initiated as early as grade 2 for the front-line management of cytokine release syndrome (CRS).

Duration of treatment: single dose treatment (2 possible re-dosings)
Screening period: 1 to 2 weeks
Lymphodepletion period: 4 days (7 days before Amendment N°9)
Treatment period: 84 days
Follow-up period: 9 months
Each patient was to participate in the study for approximately 12 months.

Criteria for evaluation:

Efficacy measurements:

The evaluation of the tumour load was performed on a BMA and the full blood count. A trephine biopsy was performed in the event of suboptimal BMA. The BMA assessed the bone marrow cellularity and blasts cells percentage.

Response including complete remission (CR), complete remission with incomplete blood count recovery (CRi), refractory disease, progressive disease and relapse disease followed the ALL guidelines. Response assessment also included molecular remission, defined as a MRD below a sensitivity threshold of 10^{-4} (<0.01%) assessed in bone marrow by FLC and/or qPCR.

CR rate, CRi rate, objective remission rate (ORR), MRD negative rate, best overall response (BOR), PFS, OS, DoR, relapse free survival (RFS) and the proportion of patients having received an allo-HSCT were analysed.

Safety measurements:

The tolerance assessment of UCART19 included throughout the study:

- 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 CRS, TLS and acute and chronic Graft-*versus*-Host Disease (GvHD) events that were graded according to the grading systems of Lee, Cairo-Bishop and Harris, respectively.
- Laboratory assessments: haematology, coagulation parameters, and biochemistry. Some laboratory parameters were graded according to the CTCAE classification version 5.0.
- Clinical examination (including weight, height, temperature and performance status), cardiac evaluation (electrocardiogram [ECG], left ventricular ejection fraction [LVEF] by echocardiography or Multi Gated Acquisition scan), and neurological consultation (mandatory for France and according to local practices for other countries).
- Vital signs (blood pressure and heart rate).
- Respiratory rate and oxygen saturation level.
- Viral/ bacterial/protozoal work up.

Biomarkers (BMK) measurements:

As this an abbreviated report, BMK assessment was limited to Interleukin (IL-) 6, IL-10, Tumour Necrosis Factor (TNF) α, Interferon (IFN) γ and the monitoring of the absence of RCL.

Pharmacokinetic (PK) measurements:

As this is an abbreviated report, no derived PK parameters were reported and only individual 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 PALL study, some data from the LTFU trial for patients previously included in PALL were considered for this CSR. They include the disposition of patients, allo-HSCT post-UCART19, new anti-leukaemic treatment, BOR, time-to-events endpoints (relapse, disease progression and death) and RCL.

Analysis Set:

- **Safety Set (SS):**

This set corresponds to all patients who received at least one course of LD treatment and one UCART19 infusion.

- **Full Analysis Set (FAS):**

Based on the intention-to-treat principle, this set corresponds to included patients who received at least one course of LD treatment and one UCART19 infusion and without relevant baseline major deviation.

During the statistics review meeting, no protocol deviations were considered as relevant.

Study patients: disposition, baseline characteristics and follow-up

Descriptive statistics were provided in patients overall.

These analyses were performed using the LD baseline (*i.e.* last reliable value prior to the start of first LD 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:
Response at D28 after the UCART19 infusion was a secondary endpoint and all other criteria evaluating the anti-leukaemic activity of UCART19 and assessments of allo-HSCT were exploratory endpoints.
Efficacy analyses were performed in the FAS overall and in the subgroup of patients having received FCA as LD treatment.
Only information from LTFU about disease progression, death, allo-HSCT and new anti-leukaemic treatment were used for activity analysis.

Safety analysis:
Descriptive statistics were provided for all safety criteria, in the SS, overall. Globally, all safety analyses were performed during the study period, except for the AESI described on each period of interest and death described on the study period and on each period of interest.
Only data issued from the case report form of PALL were considered for safety analyses, except for death.

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 13 patients were included in the PALL study. According to the number of vials used per patient (dependent upon the patient actual weight at the time of infusion and upon the dosage form), all patients received a dose of 1 to $3x10^6$ CD19CAR/RQR8$^+$_TCRαβ$^-$_T-cells /kg. Patients were followed for 4.3 months (median based on reverse Kaplan-Meier method) (range [1.2 ; 21.4 months). A total of 12 patients received FCA as LD regimen and one patient received only fludarabine/cyclophosphamide. Among the 13 patients included in the PALL study, 7 patients were included in the LTFU study and 6 patients did not enter in the LTFU study: 5 for death during PALL and 1 for investigator decision. The disposition of patients and analysis sets are presented, overall, in the following table.

Disposition of included patients and analysis sets

		All (N=13)
PALL: Included	**n**	**13**
In conformity with the protocol	n (%)	1 (7.69)
With protocol deviation(s) before or at inclusion	n (%)	12 (92.31)
Withdrawal on study treatment period* due to:	**n**	**8**
Progressive disease	n (%)	5 (62.50)
Physician decision	n (%)	3 (37.50)
Withdrawal on follow-up period* due to:	**n**	**3**
Death	n (%)	3 (100)
Completed the follow-up period*	**n**	**2**
LTFU: Included	**n**	**7 (53.85)**
Withdrawal due to:	**n**	**4**
Progressive disease	n (%)	1 (25.00)
Death	n (%)	3 (75.00)
Ongoing patients**	**n**	**3**
PALL study sets		
Included Set	n (%)	13
Safety Set	n (%)[a]	13 (100)
Full Analysis Set	n (%)[a]	13 (100)
Biomarker Evaluable Set	n (%)[b]	12 (92.3)
LTFU set		
Included Set (LTFU)	n	7

Percentages are based on n
** The study treatment and FU periods are defined as per protocol*
*** Data cut-off = 19 January 2021 (i.e. database lock of the PALL study)*
[a] *% based on the Included Set*
[b] *% based on the Safety Set*

BASELINE CHARACTERISTICS

The paediatric patients included in the PALL study were aged 0.8 to 16.6 years with a median of 4.8 years. The repartition by age group was as follows: 3 patients (23.1%) between [6-24[months, 5 (38.5%) between [2-8[years and 5 (38.5%) between [12-18[years. Seven patients were boys (53.9%), 6 were girls (46.2%) and most were White (10 patients, 76.9%). Among the 11 patients with a value at baseline, all except one had Eastern Cooperative Oncology Group Performance Status (ECOG PS) equal to 0 or 1 (value = 2 in one patient).

At study entry, the patients had suffered from B-ALL for 0.7 to 8.3 years (median = 1.9 years). According to the World Health Organization classification, 5 patients (38.5%) were diagnosed with B-ALL with t(v;11q23) considered as high cytogenetic risk, 2 patients (15.4%) with B-ALL with (12;21)(p13;q22) and 6 patients (46.2%) with B-ALL not otherwise specified. Nine patients (69.2%) had been refractory to previous treatment for 1.1 months in median (range [0.1 ; 2.6] months) and 4 (30.8%) in relapse for 0.7 months in median (range [0.4; 1.3] months). At baseline, prior to the first lymphodepletion, 6 patients (46.2%) had a BM blasts value > 50%, 4 patients (30.8%) a value in the range [5-25] % and 3 patients (23.1%) a value < 5%. Among the patients with a value at baseline, prior to the first lymphodepletion, all had a MRD > 10^{-3} assessed by qPCR and/or FLC.

All patients received drug treatment as previous therapy, 3 patients (23.1%) underwent a previous allo-graft and 2 patients (15.4%) a previous radiotherapy. Combination of therapies included combination of drug treatment with either allo-graft (3 patients, 23.1%) or radiotherapy (2 patients, 15.4%), and combination of only drugs in 8 patients (61.5%). Patients received from 2 to 7 drug treatment lines with a median of 4.0 lines and 9 patients (69.2%) 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 LD regimen in 9 patients (69.2%).

This phase I study was conducted in paediatric patients with R/R CD19 positive B-ALL, for which baseline characteristics were broadly in accordance with the target population defined in the study protocol.

EXTENT OF EXPOSURE

All patients had a relative volume administered of UCART19 equal to 100% of the intended volume. No patient had re-dosing with UCART19 within the framework of the PALL study or in compassionate use program.

EFFICACY RESULTS

Among the 13 patients of the FAS, 6 (46.2%) were considered as responders post-UCART19 infusion, with as **best overall response** (across all time points after the UCART19 infusion): MRD negative CRi in 4 patients (30.8%), MRD negative CR in 1 patient (7.7%) and morphologic CRi in 1 patient (7.7%).
Six patients (46.2%) were non-responders with as BOR: refractory disease in 4 patients (30.8%), relapse disease and progressive disease in 1 patient (7.7%) each.
One patient was non-evaluable for the BOR because he received anti-leukaemic treatment prior D28 response assessment.

Thus, according to BOR post-UCART19 infusion, the **objective response rate** was 46.2% (6 patients, 95% CI [19.22;74.87]) with 38.5% for CRi rate (5 patients, 95% CI [13.86;68.42]) and 7.7% for CR rate (1 patient, 95% CI [0.19;36.03]).
Among the 6 patients with an objective remission, the MRD negative rate was 83.3% (5 patients, 95% CI [35.88;99.58]).

At D28 (in intent to treat) after the UCART19 infusion, the ORR was 53.9% (7 patients, 95% CI [25.13 ; 80.78]), all in CRi.
Among the 7 patients with an objective remission, the MRD negative rate was 71.4% (5 patients, 95% CI [29.04 ; 96.33]).

The median of the **progression free survival** post-UCART19 infusion was estimated at 3.0 months (95% CI [1.1;5.1]) with analysis ignoring allo-HSCT and 1.8 months (95% CI [1.1;1.8]) with analysis censoring at the time of allo-HSCT.
Progression free survival rate at 3 months was 50% (95% CI [21%;74%]) and progression free survival rates at 6 months and 12 months were both 25% (95% CI [6%;50%]) (analysis ignoring allo-HSCT).

The median of the **overall survival** was estimated at 5.2 months (95% CI [3.6;.]). The survival rate at 6 months was 42% (95% CI [16%;67%]) and the survival rate at 12 months was 25% (95% CI [6% ; 51%]).

Among the 6 responder patients post-UCART19 infusion, **relapse free survival** rate at 3 months was 100% and relapse free survival rates at 6 months and 12 months were both 50% (95% CI [11%;80%]) (analysis ignoring allo-HSCT).

A total of 6 patients (46.2%, all responder patients) received one **allo-HSCT** post-UCART19 infusion, considering only patients grafted before new anti-leukaemic treatment.

SAFETY RESULTS

- **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

		ALL
PALL study	**N**	**13**
Patients having reported at least one:		
Emergent Adverse Event (EAE)	n (%)	13 (100)
EAE related to at least UCART19	n (%)	12 (92.3)
Severe EAE (grade ≥ 3)	n (%)	13 (100)
Severe EAE (grade ≥ 3) related to at least UCART19	n (%)	8 (61.5)
Serious EAE (including death)	n (%)	13 (100)
Serious EAE related to at least UCART19	n (%)	10 (76.9)
Patients who died (during PALL study)	n (%)	5 (38.5)
LTFU study	**N**	**7**
Patients who died (during LTFU study)	n (%)	4 (57.1)

** Study period lymphodepletion period + treatment period + follow-up period*

All patients of the Safety Set reported at least one EAE during the study period. A total of 215 EAEs were reported.

The ***most frequently affected System Organ Classes*** (≥ 60% of patients, *i.e.* reported in at least 8 patients) during the study period were Immune system disorders (84.6% of patients, 11 patients), Infections and infestations (76.9%, 10 patients), Blood and lymphatic system disorders, Metabolism and nutrition disorders (69.2%, 9 patients, each), Gastrointestinal disorders and Investigations (61.5%, 8 patients, each).

The ***most commonly reported EAEs*** (≥ 20% of patients, *i.e.* reported in at least 3 patients) during the study period were CRS (84.6% of patients, 11 patients), hypokalaemia (61.5%, 8 patients), anaemia (46.2%, 6 patients), infusion-related reaction, neutropenia, thrombocytopenia (38.5%, 5 patients, each), acute GvHD in skin, cytopenia (corresponding to Lowest Level Term Prolonged cytopenia as per protocol definition), hypophosphatemia, neutrophil count decreased (30.8%, 4 patients, each), activated partial thromboplastin time (aPTT) prolonged, acute lymphocytic leukaemia recurrent, BK virus infection, confusional state, hypertension, international normalized ratio (INR) increased, neurotoxicity, platelet count decreased, serum ferritin increased and viral haemorrhagic cystitis (23.1%, 3 patients, each).

All patients reported at least one severe EAE (CTCAE grade ≥ 3). A total of 97 severe EAEs were reported during the study period. The ***most commonly reported severe EAEs*** (≥ 20% of patients *i.e.* reported in at least 3 patients) during the study period were hypokalaemia (61.5% of patients, 8 patients), anaemia, neutropenia, thrombocytopenia (38.5%, 5 patients, each), prolonged cytopenia, hypophosphatemia, neutrophil count decreased (30.8%, 4 patients, each), acute lymphocytic leukaemia recurrent and CRS (23.1%, 3 patients, each).

All patients except one (*i.e.* 92.3% of patients) experienced at least one EAE considered to be related to at least UCART19 during the study period. A total of 93 EAEs related to at least UCART19 were reported. The ***most commonly reported EAEs related to at least UCART19*** (≥ 20% of patients *i.e.* at least 3 patients) during the study period were CRS (84.6% of patients, 11 patients), hypokalaemia (30.8%, 4 patients), neurotoxicity and serum ferritin increased (23.1%, 3 patients, each).

A total of 8 patients (61.5%) had 29 severe EAEs related to at least UCART19 during the study period. The ***most commonly reported severe EAEs related to at least UCART19*** (≥ 15% of patients *i.e.* at least 2 patients) during the study period were hypokalaemia (30.8%, 4 patients), CRS (23.1%, 3 patients), hypophosphatemia and mouth haemorrhage (15.4%, 2 patients, each).

The 13 patients of the Safety Set experienced at least one serious emergent adverse event (SEAE) (including death) during the study period. A total of 109 SEAEs were reported. The ***most commonly reported SEAEs*** (≥ 20% of patients, *i.e.* at least 3 patients) during the study period were CRS (76.9% of patients, 10 patients), neutropenia (38.5%, 5 patients), prolonged cytopenia, infusion related reaction (30.8%, 4 patients, each), acute lymphocytic leukaemia recurrent and hypokalaemia (23.1%, 3 patients, each).

A total of 10 patients (76.9%) reported 39 ***SEAEs related to at least UCART19*** during the study period, mainly CRS (76.9%, 10 patients) and hallucination (15.4%, 2 patients). All the other SEAEs related to at least UCART19 were reported once. No serious infusion related reaction was related to UCART19.

A total of ***5 patients (38.5%) died during the PALL study***, of which 1 patient died of pulmonary mucormycosis during the post-UCART19 period, considered as related only to lymphodepletion, and 4 patients died during the FU period, of acute lymphocytic leukaemia recurrent (2 patients), malignant neoplasm progression and thrombotic microangiopathy (one patient each), not considered as related to UCART19 or to lymphodepletion.

In addition, at the time of the database lock of the PALL study (*i.e.* 19 January 2021), ***4 patients (57.1%)*** of the 7 patients included in the LTFU study ***died during the LTFU study***, of malignant neoplasm progression (one patient), multiple organ dysfunction syndrome (one patient), malignant neoplasm progression and respiratory failure (one patient), and respiratory tract infection fungal (one patient). All the fatal events were considered as not related to UCART19.

It should be noted that one patient was withdrawn from the PALL study for physician decision (refractory disease) and did not enter in the LTFU study (investigator decision), so the death status for this patient is unknown.

- **AE of special interest**

During the post-UCART19 treatment period

A total of 11 patients (84.6%) out of 13 patients treated with UCART19 experienced 11 *cytokine release syndrome* during the post-UCART19 period, all related to at least UCART19. Three events in 3 patients (23.1%) were rated severe (all grade 3) and 10 events in 10 patients (76.9%) were serious.

One patient (7.7%) suffered from *acute graft versus host disease in skin*, grade 1, serious and related to at least UCART19 during the post-UCART19 period.

A total of 8 patients (61.5%) presented 25 *neurologic events* during the post-UCART19 period, mainly (≥ 2 patients) neurotoxicity, confusional state (3 patients each, 23.1%), headache and hallucination (2 patients each, 15.4%). No event was severe and 10 events in 3 patients (23.1%) were serious. All events except 2 (one case of confusional state and major depression in the same patient) were related to at least UCART19.

Regarding *B cell aplasia and resultant hypogammaglobulinemia*, a total of 4 patients (30.8%) experienced 3 prolonged cytopenia (all severe [grade 4], serious, 1 event related to UCART19 and LD and 1 event related to only LD) and 1 hypogammaglobulinemia (non-severe, non-serious and not related to UCART19).

A total of 10 patients (76.9%) presented 20 events of *infection* during the post-UCART19 period, mainly (≥ 2 patients) BK virus infection, viral haemorrhagic cystitis (3 patients each, 23.1%) and cytomegalovirus infection reactivation (2 patients, 15.4%). Twelve events in 7 patients (53.8% of patients) were severe (all rated grade 3 except pulmonary mucormycosis rated grade 5 [fatal, as previously described]) and 14 events (including the 12 severe events) in 8 patients (61.5%) were serious. A total of 2 patients (15.4%) had 5 events of infection related to at least UCART19.

No case of *immediate infusion-related reaction* or *tumour lysis syndrome* was reported during the post-UCART19 period.

During the follow-up period

Concerning *new malignancy*, among the 10 patients of the FU period, 2 patients (20.0%) presented with acute lymphocytic leukaemia recurrent. These events were linked to the studied disease, they were severe, serious, not-related to UCART19 and led to death (already described previously).

A total of 5 patients (50.0%) experienced 11 *new haematologic disorders* during the FU period including acute lymphocytic leukaemia recurrent (2 fatal cases, already described above), INR increased (2 cases in the same patient), thrombotic microangiopathy (fatal case, already described previously), anaemia, febrile neutropenia, aPTT prolonged, neutrophil count decreased, ecchymosis and petechiae (one case each). All these events except anaemia and one case of INR increased were severe and serious. aPTT prolonged, one case of INR increased, ecchymosis and petechiae (all in the same patient) were related to at least UCART19.

Three patients (30.0%) experienced 7 *neurologic events* during the FU period including cerebral haemorrhage, encephalopathy, intraventricular haemorrhage, lethargy, posterior reversible encephalopathy syndrome, seizure and depression. The case of posterior reversible encephalopathy syndrome was severe (grade 3) and all events except depression were serious. Cerebral haemorrhage and encephalopathy (in the same patient) were related to at least UCART19.

No case of *autoimmune disorder*, *B-cell aplasia* or *AE assessed as related to UCART19* was reported during the FU period.

During the treatment and follow-up period
A total of 3 patients (23.1%) experienced 3 *prolonged cytopenia* during the post-UCART19 and FU period, already described previously in paragraph "B-cell aplasia and resultant hypogammaglobulinemia occurring on the post-UCART19 period".

- **Blood parameters rated severe (grade 3 or 4) according to the CTCAE version 5.0 grading**

Emergent severe abnormal biochemical values were sparsely distributed among the following biochemical parameters: high aspartate aminotransferase (3 patients, 27.3%), high gamma-glutamyl transferase (GGT) (2 patients, 18.2%), high alanine aminotransferase (1 patient, 9.1%), high creatinine (1 patient, 7.7%) and low calcium (1 patient, 7.7%). All emergent severe abnormal values were rated grade 3 except in one patient with high GGT rated grade 4.

Emergent severe abnormal haematological values were observed for low platelets (84.6% of patients, 11 patients, all grade 4), low haemoglobin (69.2% of patients, 9 patients, all grade 3), low lymphocytes (61.5% of patients, 8 patients, all grade 4), low white blood count (46.2% of patients, 6 patients, all grade 4), low neutrophils (38.5% of patients, 5 patients, including one patient with value rated grade 3 and 4 patients with grade 4) and high haemoglobin (8.3%, 1 patient, grade 3).

Emergent severe abnormal values for coagulation parameters were observed for low fibrinogen (41.7% of patients, 5 patients including 3 patients with value rated grade 3 and 2 patients with grade 4).

- **Other safety evaluation**

Vital signs, clinical examination and ECOG performance status
No clinically relevant median change over time considering the last post-baseline value was observed for any parameter including *weight, body temperature, blood pressure, heart rate, respiratory rate and oxygen saturation*.
Regarding *ECOG performance status*, a total of 7 patients (53.8%) had a worsening from baseline to post-baseline, considering the worst (highest) post-baseline value: from ECOG PS 0 to 1 in 4 patients (30.8%), from 0 to 2 in 1 patient (7.7%), from 1 to 3 in 1 patient (7.7%) and from 2 to 4 in 1 patient (7.7%). In addition, 2 patients (15.4%) with a missing value at baseline had ECOG PS superior to 0 at the worst post-baseline value (ECOG PS = 1 for one and ECOG PS = 3 for the other).

Electrocardiogram
One patient (7.7%) had at least one ECG abnormality considered as clinically significant by the investigator during the study period.

LVEF
All patients assessable at baseline (n = 12) had an LVEF ≥ 50%.
At the end of study, the only 2 assessable patients had an LVEF ≥ 50%. Their change from baseline to end of the study was -4.0% and 8.0%, respectively.

Infections

A total of 5 out of 13 patients (38.5%) had clinically significant viral abnormalities and 1 out of 9 patients (11.1%) had clinically significant bacterial abnormalities during the study period.

BMK RESULTS
In the BMKES, the concentrations of **main circulating proteins** (IL-6, IL-10, TNFα and IFNγ) measured by multiplex Meso Scale Discovery immunoassay were in the assay range at each visit in assessable patients, except for IFNγ at D28 (one patient with a value < Lower Limit of Quantification). Patients with severe CRS (≥ grade 3) tended to show higher peaks of IL-10 and IFNγ than patients with CRS grade [0-2], mainly between D5 and D14. Results should however be interpreted with caution due to the limited number of patients with a severe CRS (n = 2) among the assessable patients.
No **replication competent lentivirus** was detected in tested patients by vesicular stomatitis virus G glycoprotein qPCR at each visit. Due to some patients not rolled over to the LTFU study and the COVID-19 situation, full RCL monitoring profile during the first year following the last UCART19 infusion was not always available.

CONCLUSION

This phase I, open-label, non-comparative, first-in-human paediatric PALL study was conducted in 13 paediatric patients aged 0.8 to 16.6 years with relapsed or refractory CD19-positive B-ALL to evaluate the safety of UCART19 (S68587), given as single infusion.

At D28 after the UCART19 infusion, the objective response rate (CR or CRi) was 53.9% (7 patients, 95% CI [25.13 ; 80.78]), all in CRi. In these patients, the MRD negative rate was 71.4% (5 patients, 95% CI [29.04 ; 96.33]).

According to the best overall response (across all time points after the UCART19 infusion), the objective response rate was 46.2% (*i.e.* 6 responder patients, 95% CI [19.22;74.87], 5 patients in CRi and 1 in CR) with a MRD negative rate of 83.3% (5 patients, 95% CI [35.88;99.58]). The relapse free survival rate of the 6 responder patients was 100% at 3 months and 50% (95% CI [11%;80%]) at 6 and 12 months (analysis ignoring allo-HSCT).

Considering all patients, the progression free survival rate was 50% (95% CI [21%;74%]) at 3 months and 25% (95% CI [6%;50%]) at 6 months and 12 months (analysis ignoring allo-HSCT).

All patients reported at least one severe EAE (grade ≥ 3 according to CTCAE) during the study period, mainly (≥ 4 patients) hypokalaemia (61.5% of patients), anaemia, neutropenia, thrombocytopenia (38.5% each), prolonged cytopenia, hypophosphatemia and neutrophil count decreased (30.8% each). All patients except one (*i.e.* 92.3% of patients) experienced at least one EAE considered to be related to at least UCART19, mainly (≥ 4 patients) CRS (84.6%) and hypokalaemia (30.8%). All patients experienced at least one SEAE (including death), mainly (≥ 4 patients) CRS (76.9%), neutropenia (38.5%), prolonged cytopenia and infusion related reaction (30.8% each). A total of 9 patients died (during the PALL and LTFU studies). No replication competent lentivirus was detected throughout the patient follow-up (when testing was possible).

After 13 patients treated with UCART19, the sponsor decided not to enrol any new patient in the PALL study as the development strategy was reviewed and the decision was to stop the development of S68587 in the indication of R/R B-ALL. This decision was not due to safety concerns.

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