Stockholm - June 14-17, 2018

CALM study

Phase I study of UCART19, an allogeneic anti-CD19 CAR T-cell product, in high risk adult patients with CD19+ relapsed/refractory (R/R) B-cell ALL: Preliminary results of phase I CALM study

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BACKGROUND

UCART19 is a second generation anti-CD19 CAR (anti-CD19 scFv- 41BB- CD3z), that has been genetically modified to disrupt the T-cell receptor alpha constant (TRAC) and CD52 genes with the help of mRNA coding for transcription activator-like effector nuclease (TALEN®), a Cellectis gene-editing technology (Figure 1).

UCART19 is expressing a RQR8 "safety switch" intended to allow targeted elimination of RQR8+ cells by rituximab.

This is a ready-to-use, off-the-shelf therapy that has the advantage that peripheral blood mononuclear cells (PBMCs) isolated from a single healthy donor can be used to treat multiple patients

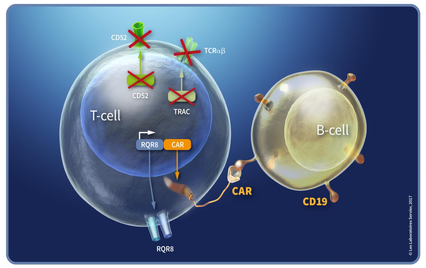

Figure 1. UCART19, an engineered allogeneic anti-CD19 CAR T-cell medicinal product

As previously reported with Cellectis, preliminary efficacy for UCART19 was demonstrated with two infants suffering from R/R ALL. Both infants were treated with UCART19 under a special license granted by the Medicines and Healthcare Products Regulatory Agency (MHRA). Both infants remain in remission 24 and 30 months after subsequent transplant.

Updated data for UCART19 administered to a pediatric population suffering from R/R ALL (PALL study) are presented in EHA 2018 (abstract #PF175).

METHODS

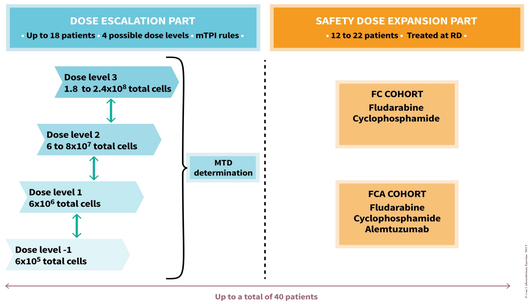

Figure 2. Study plan

- Phase I multicenter, dose-escalating, open-label, non-comparative study, to evaluate up to 4 dose levels (DL) of UCART19 and to determine the maximum tolerated dose (MTD) in adult patients with R/R B-ALL.
- Dose-escalation is followed by a safety expansion part, patients dosed at MTD or at the recommended dose (RD) (Figure 2)
- The lymphodepletion (LD) regimen starts from D-7 preceding UCART19 infusion and combines: cyclophosphamide 1500 mg/m² and fludarabine 90 mg/m², without alemtuzumab (FC) or with alemtuzumab 1 mg/kg (FCA)
- During the expansion part, the role of alemtuzumab will be investigated in 2 cohorts of patients (LD with FC or FCA)
- At D0, UCART19 is administered as a single non-split dose, by slow IV infusion (5 minutes)
- Evaluation of dose limiting toxicities is performed 28 days after infusion (D28)
- Bone marrow aspiration/biopsy is performed before LD, at D-1, at D28 and D84
- Minimal residual disease (MRD) is defined by < 10^{-4} blasts in bone marrow, assessed by flow cytometry (FLC) and/or by qPCR
- At study completion (D84 after infusion), the patient is rolled-over to the long term follow-up study (LTFU) for a 15-year duration

OBJECTIVES

Primary objective

- To evaluate the safety and tolerability of UCART19 and to determine the maximum tolerated dose (MTD) in relapsed or refractory B-ALL adult patients

Secondary objective

- To assess the anti-leukemic activity:
  - ✓ rate of objective response at Day 28, Day 84 and overall,
  - ✓ duration of response, time to remission, progression free survival

Exploratory objectives

- To assess the proportion of patients who underwent an allogeneic stem cell transplant (allo-SCT) at Day 84.
- To analyse the expansion, phenotype, trafficking and persistence of UCART19 in blood, in bone marrow

KEY ELIGIBILITY CRITERIA

Inclusion criteria

- Age ≥ 16 years
- Patient with R/R CD19 positive B-ALL
  - ✓ Morphological disease or MRD⁺ (≥ $1x10^{-3}$ by flow cytometry (FLC) and/or qPCR)
  - ✓ Who has exhausted available treatment options

Exclusion criteria

- Previous treatment with investigational gene or cell therapy medicine products
- Active systemic infection
- Active CNS leukemia
- Extra-medullary disease

RESULTS

STUDY STATUS

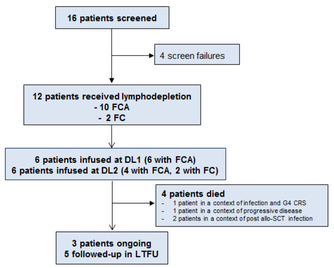

Figure 3. Study status

- As of April 24, 2018, 12 patients have been treated in the dose escalation part, with 6 patients at DL1 with $6x10^6$ total cells (approximately $1x10^5$ cells/kg) and 6 patients at DL2 with 6 to $8x10^7$ total cells (approximately $1x10^6$ cells/kg). Patient characteristics are presented in Table 1.
- 4 patients had recurrent genetic abnormalities including hyperdiploidy and translocations
- Patients had received a median of 3.5 prior treatment lines (range 1-5)
- Recruitment in dose escalation is active in 3 countries (UK, U.S. and France)

SAFETY

N=12	Worst grade G1 n (%)	G2 n (%)	G3 n (%)	G4 n (%)	G5 n (%)	All grades n (%)
AEs related to UCART19						
Cytokine release syndrome	1 (8.3)	8 (66.7)	1 (8.3)	1 (8.3)	-	11 (91.7)
Neurotoxicity events	3 (25)	-	-	-	-	3 (25)
Graft-versus-host disease in skin	1 (8.3)	-	-	-	-	1 (8.3)
AEs related to lymphodepletion and/or UCART19						
Prolonged cytopenia*	-	-	-	3 (25)	-	3 (25)
Neutropenic sepsis	-	-	-	1 (8.3)	1(8.3)	2 (16.7)
CMV infection	-	3 (25)	-	-	-	3 (25)
Adenovirus infection	1 (8.3)	-	1 (8.3)	-	-	2 (16.7)

* Persistent Grade 4 neutropenia and/or thombocytopenia beyond Day 42 post UCART19 infusion, except if >5% bone marrow blasts
n: number of patients with at least one event by worst grade

Table 2. Most relevant AEs post-UCART19 infusion/ before allo-SCT

- 11/12 patients experienced CRS (G1 to G4) (Table 2) .
  - ✓ Tocilizumab was administered in 6/11 patients
  - ✓ CRS correlated with serum cytokine increase (IL-6, IL-10 and IFNγ) and UCART19 expansion in blood in all patients but one
- 1 patient developed G1 skin GvHD at D31, that resolved with topical steroids
- Viral reactivations (CMV and/or adenovirus) occurred in 4 patients (G1 to G3)
- 3/12 patients developed prolonged cytopenia defined as persistent grade 4 beyond D42 post UCART19
- 2 DLTs have been observed, one at DL1 related to UCART19: G4 CRS associated with G5 neutropenic sepsis (death at D15 post-infusion) and one at DL2 related both to UCART19 and LD: G4 prolonged cytopenia associated with infection and pulmonary hemorrhage (death at D82 post-infusion)
- Deaths: 4 deaths have been reported: 1 patient with CRS G4 associated with infection, 1 patient had progressive disease and 2 patients in a context of post allo-SCT infection

BASELINE CHARACTERISTICS

	All (N=12)
Median age in yrs (range)	29.50 [18-62]
Nb of prior treatment lines	
1 or 2	4
≥3	8
incl. prior inotuzumab ozogamicin	6
incl. prior blinatumomab	3
Previous allo-SCT	7
Time of relapse following previous allo-SCT	
< 6 months	4
≥ 6 months	3
Median (range)	5.9 months (4.1-11)
Bone marrow blasts prior to lymphodepletion	
<5%	3
5-25%	3
>25%	6
Median (range)	34% (0-98)

Table 1. Patient characteristics

UCART19 KINETICS

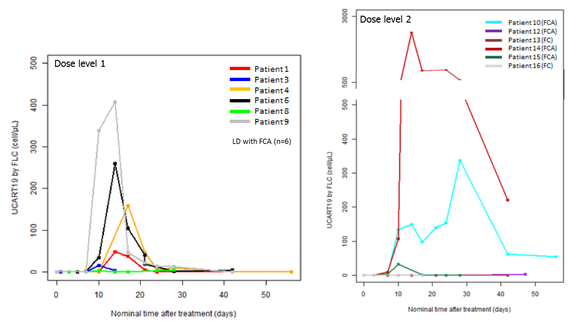

Figure 5. Flow cytometry PK profile

- Preliminary data on flow cytometry at DL1 and DL2 show that UCART19 was detectable in blood from D3 to D14 with a proliferation peak between D10 and D17. One patient at DL2 showed the highest peak linked to longest persistence (Figure 5)
- Among those patients with cell expansion, at DL1: 1 patient showed UCART19 persistence up to D42; at DL2: 2 patients showed persistence up to D42 and ongoing persistence at D56
- Preliminary data suggests that the level of UCART19 expansion does not correlate with response on D28; instead, MRD⁻ CR at D28 was observed even with low levels of UCART19 expansion
- After the first dose of UCART19, no expansion was observed in 2 out of 10 patients who received LD with FCA and 2 out of 2 patients who received FC
- The role of alemtuzumab in UCART19 expansion is under investigation.

RESULTS

ANTI-LEUKEMIC ACTIVITY

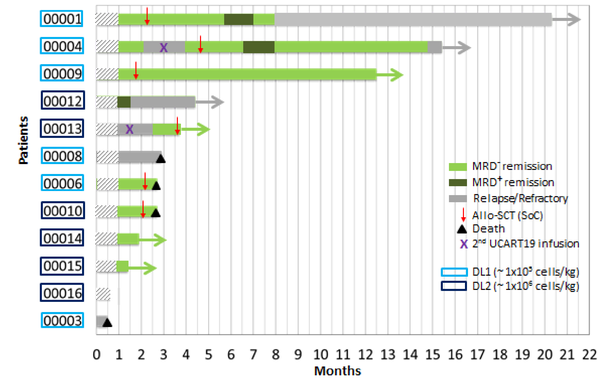

Figure 4. Anti-leukemic activity

- 12 patients received at least one UCART19 infusion as of April 24, 2018
- 10/12 patients were evaluable for anti-leukemic activity at D28 post UCART19 infusion. One patient died at D15 and one patient did not reach D28 evaluation
- At D28, 8 out of 10 evaluable patients achieved CR, including 7 patients in MRD⁻ CR. Those 2 patients with refractory disease had no UCART19 expansion
- 4 out of 7 patients in MRD⁻ CR underwent an allo-SCT. One patient remains in MRD⁻ CR 12.4 months post UCART19 infusion, one patient relapsed 100 days post transplant
- Re-dosing with UCART19 was permitted on a compassionate use basis:
  - ✓ The 1st patient had relapsed with CD19⁺ disease at D61 following 1st dose (LD with FCA); the 2nd dose (LD with FC) allows this patient to achieve MRD⁻ at D28
  - ✓ The 2nd patient had no UCART19 expansion after the 1st dose (LD with FC) and had refractory disease at D28; the 2nd dose (LD with FCA) allows this patient to achieve MRD⁻ at D28
  - ✓ Both patients proceeded subsequently to an allo-SCT
- 4 patients remain in molecular remission at data cut-off

CONCLUSIONS

- **First allogeneic, off-the-shelf, CAR T-cell therapy in high risk, heavily pretreated, R/R adults B-ALL**
- **All patients but one experienced manageable CRS, grade 1 neurotoxicity and skin GVHD were observed in 3 and 1 patients, respectively**
- **10 out of 12 patients were evaluable for anti-leukemic activity at D28 post UCART19, one patient did not reach D28 evaluation**
- **8 out of 10 evaluable (80%) patients achieved CR at D28 (88% MRD⁻ CR)**
- **2 patients received a 2nd dose of UCART19 (off-protocol), whom both achieved MRD⁻ CR at D28**
- **6 patients proceeded to an allo-SCT, including 4 patients after the 1st dose of UCART19, and 2 patients after the 2nd dose**
- **4 patients remain in MRD⁻ CR at 12.4, 3.6, 1.8 and 1.3 months respectively, post UCART19**
- **Viral complications and prolonged cytopenia were encountered related to lymphodepletion and/or UCART19**

ACKNOWLEDGEMENTS

Patients and their families participating in this early phase trial.
Nurses, study personnel and investigators working with us on the study.
Teams involved in UCART19 studies at Servier and Allogene Therapeutics.
TALEN® is a proprietary technology owned by Cellectis.

Disclaimer: Part of these data were presented during an oral session at the EBMT congress on 21 March, 2018.

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PALL Study

Phase I study of UCART19, an allogeneic anti-CD19 CAR T-cell product, in high risk pediatric patients with CD19+ relapsed/refractory (R/R) B-cell ALL: Preliminary results of PALL study

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Poster # PF175

BACKGROUND

UCART19 is a genetically modified CAR T-cell product manufactured from healthy donor cells expressing:

- a second generation anti-CD19 CAR (anti-CD19 scFv- 41BB- CD3z), and
- a RQR8 «safety switch» intended to allow targeted elimination of RQR8+ cells by rituximab.

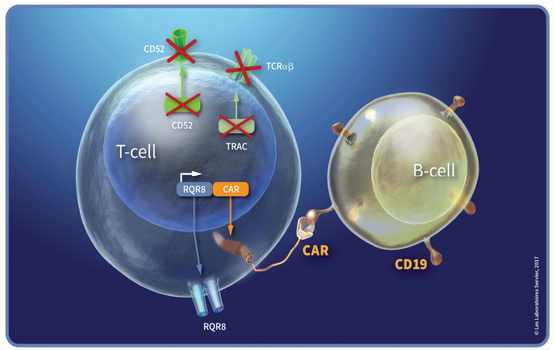

Figure 1. UCART19, an engineered allogeneic anti-CD19 CAR T-cell medicinal product

In addition, UCART19 has been modified to disrupt the T-cell receptor alpha constant (TRAC) and CD52 genes with the help of mRNA coding for transcription activator-like effector nuclease (TALEN®), Cellectis' gene-editing technology.

UCART19 is a ready-to-use, off-the-shelf therapy that has the added advantage that peripheral blood mononuclear cells (PBMCs) isolated from a single healthy donor can be used to treat multiple patients.

As previously reported with Cellectis, preliminary efficacy for UCART19 was demonstrated the with two infants with R/R ALL, Both infants were treated with UCART19 under a special license granted by the Medicines and Healthcare Products Regulatory Agency (MHRA). Both infants remain in remission 24 and 30 months after subsequent transplant.

METHODS

OBJECTIVES

Primary objective

- To evaluate the safety of UCART19 at a fixed dose in pediatric patients with relapsed or refractory B-ALL

Secondary objective

- To determine the ability of UCART19 to achieve molecular remission at D28

Exploratory objectives

- To determine the ability of UCART19 to achieve molecular remission at D56, D84 or ahead of allo-SCT conditioning regimen initiation
- To assess the remission rate, duration of remission, time to remission, disease specific survival, and progression free survival
- To assess the proportion of patients who underwent allo-SCT
- To analyse the expansion, phenotype, trafficking and persistence of UCART19

KEY ELIGIBILITY CRITERIA

Inclusion criteria

- Age between 6 months and < 18 years old
- Patient with CD19+ R/R B-ALL
  - Morphological or MRD+ (≥ $1x10^{-3}$ by flow cytometry and/or qPCR)
  - Who have exhausted available treatment options
- Eligible for allo-SCT with suitable donor available

Exclusion criteria

- No previous treatment with investigational gene or cell therapy products
- No active infection
- No active CNS leukemia

METHODS

This is a phase I multicenter, open-label, non-comparative study to evaluate the safety and the ability of UCART19 to induce molecular remission at day (D) 28 and enable allogeneic stem cell transplantation (allo-SCT) in pediatric patients with high-risk relapsed or refractory (R/R) CD19+ B-ALL.

The lymphodepletion regimen starts from D-7 (during the week preceding UCART19 infusion) and combines:

- cyclophosphamide (C) (60 mg/kg/day for 2 days),
- fludarabine (F) (30 mg/m²/day for 5 days),
- w/wo alemtuzumab (A) (0.2 mg/kg/day for 5 days).

At D0, a flat dose of UCART19 ($2x10^7$ total cells equivalent to 1.1 to $2.3x10^6$ cells/kg) is administered as a single non-split dose, by slow IV infusion over 5 minutes.

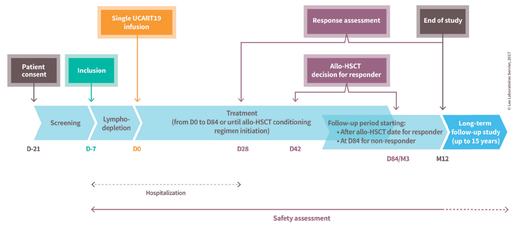

Figure 2. Study design

Safety assessment is performed at D28 post UCART19 administration.

BMA is performed at baseline, D-1, D14 (optional), D28, D56, D84 or ahead of allo-SCT conditioning regimen initiation or at the withdrawal visit (at the investigator's discretion).

During the 12-month follow-up period, a BMA will be performed at M1, M2, M3, M6 and M12 post allograft for the disease assessment.

For refractory patients, the BMA will be performed optionally according to investigator's judgment.

RESULTS

As of April 24, 2018, a total of 6 R/R ALL pediatric patients have been treated in the study. Patients' characteristics are presented in Table 1.

	All (N=6)
Median age (range)-Years	3.75 [0.8-16.4]
Disease at screening	
B-ALL relapsed	6
Disease at diagnosis	
NOS	4
with t(12;21)(p13;q22) TEL-AML1 (ETV6-RUNX1)	1
with t(v;11q23);MLL rearranged	1
Nb of prior treatment lines	
2 prior treatment lines	1
3 prior treatment lines	2
≥4 prior treatment lines	3
Previous inotuzumab ozogamicin	2
Previous allogeneic stem cell transplantation (SCT)	2
Time of relapse following previous SCT	
>6 months	2
Bone marrow blasts at inclusion	
<10%	5
>50%	1

Table 1. Patients characteristics

STUDY STATUS

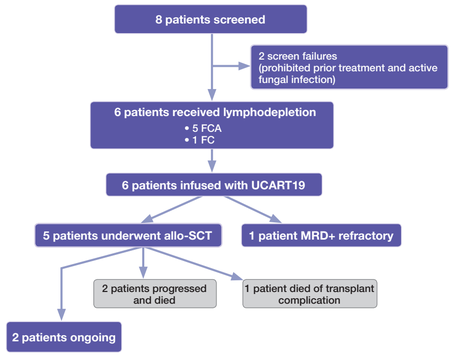

Figure 3. Study status

SAFETY

As detailed in Table 2, the most frequent AE related to UCART19 were cytokine release syndrome (CRS), neurotoxic events and skin GvHD; prolonged cytopenia were reported as related to lymphodepletion and in some cases possibly related to UCART19; viral reactivation (CMV, ADV, BK, metapneumovirus) was reported as related to lymphodepletion.

n = number of patients with at least one event by worst grade

All (N=6)	Worst grade G1 n (%)	G2 n (%)	G3 n (%)	G4 n (%)	All grades
AEs related to UCART19					
Cytokine release syndrome	1 (17)	4 (67)	1 (17)	-	6 (100)
Neurotoxic events	2 (33)	1 (17)	-	-	3 (50)
Graft-versus-host disease*	1 (17)	-	-	-	1 (17)
AEs related to lymphodepletion and/or UCART19					
Prolonged cytopenia**	-	-	-	3 (50)	3 (50)
BK virus hemorrhagic cystitis	-	-	2 (33)	-	2 (33)
Metapneumovirus infection	-	-	-	1 (17)	1 (17)
CMV infection	-	-	1 (17)	-	1 (17)
Febrile neutropenia	-	-	1 (17)	-	1 (17)
Adenovirus infection	1 (17)	-	-	-	1 (17)

*Acute cutaneous GvHD
** Persistent Grade 4 neutropenia and/or thombocytopenia beyond Day 42 post UCART19 infusion, except if >5% bone marrow blast

Table 2. Most frequent AE post-UCART19 infusion/before allo-SCT

ANTI-LEUKEMIC ACTIVITY

All patients completed the 28-day evaluation period and were evaluable for anti-leukemic activity. 5/6 pts had achieved complete remission with incomplete blood count recovery and were MRD negative (<0.01%) by flow cytometry or qPCR. Three patients died post-transplant, 2 for progression and one died in remission due to transplant complications.
Alemtuzumab's benefit/risk in lymphodepletion prior to UCART19 is under investigation.

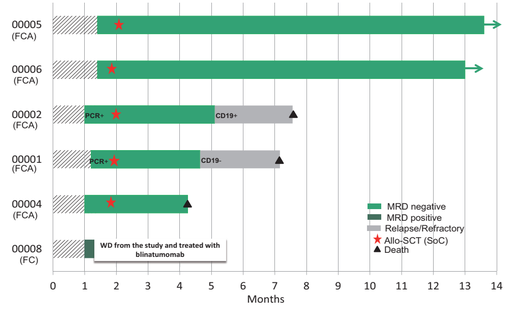

Figure 4. Anti-leukemic activity

RESULTS

PRELIMINARY CELLULAR KINETICS

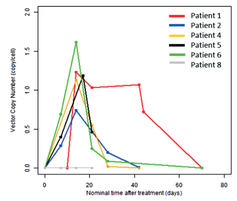

Figure 5. VCN data in blood

UCART19 vector copy number (VCN) are measured in blood and bone marrow by qPCR. Preliminary data showed that for 5 out of 6 patients, UCART19 was detectable in blood by D7, with a proliferation peak observed around D14. No UCART19 was detected for one patient who subsequently relapsed. For 3 out of 5 patients, UCART19 persisted in blood until D28. For 2 out of 5 patients, UCART19 remained detectable in blood on D42. Persistence beyond D42 was not measured since UCART19 was eliminated by conditioning regimen for allo-SCT.

CYTOKINES KINETICS

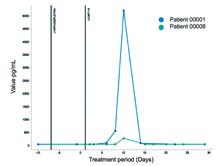

Figure 6. Levels of IFNγ in two patients

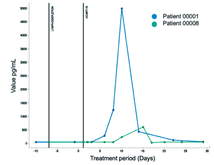

Figure 7. Levels of IL-6 in two patients

2 out of 6 patients had IL-6 and IFNγ elevation. No cytokine elevation was observed in 4 out of 6 patients by local lab. All 6 patients experienced CRS. CRS G3 was observed in patient 1 and CRS G2 in patient 8. Time to onset of first CRS symptoms ranged between D5 and D9.

CHIMERISM DATA

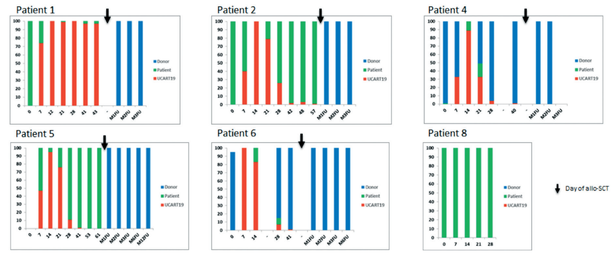

Figure 8. Chimerism data in blood

UCART19 was detectable in blood from D7 to at least D42 in all patients but one by molecular signatures of T-cell donor chimerism.

CONCLUSION

- **First allogeneic, off-the-shelf, CAR T-cell therapy in high risk, heavily pretreated, R/R pediatric B-ALL.**
- **To date UCART19 related toxicities have been manageable:**
  - **Grade 1 acute GvHD (restricted to skin) observed in one patient and resolved with topical steroids.**
  - **Grade 3 CRS observed in one patient and resolved within 13 days following treatment with tocilizumab.**
  - **No grade 3/4 neurotoxicity reported.**
- **UCART19 has resulted in flow cytometry MRD- CR in 5/6 patients.**
- **Lymphodepletion-related viral complications and prolonged cytopenia were encountered.**
- **Two patients are still in remission > 13 months post-UCART19 infusion.**

ACKNOWLEDGEMENTS

Patients and their families participating in this early phase trial.
Nurses, study personnel and investigators working with us on the study.
Teams involved in UCART19 studies at Servier and Allogene Therapeutics.
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