Clinical trial SUMMARY

Short study title

A study to evaluate the safety and tolerability of ascending doses of UCART19 given as a single infusion in patients with relapsed/refractory (R/R) B-cell acute lymphoblastic leukaemia (B-ALL) and to determine the maximum tolerated dose (MTD).

Full scientific title:

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).

In this summary:

Therapeutic area:
Oncology

Indication:
Acute lymphoblastic leukaemia

Study phase:
Phase 1

08 September 2021
Final version

CLINICAL TRIAL SUMMARY

A study to evaluate the safety and tolerability of ascending doses of UCART19 given as a single infusion in patients with relapsed/refractory (R/R) B-cell acute lymphoblastic leukaemia (B-ALL) and to determine the maximum tolerated dose (MTD).

We would like to thank all the patients who participated in the study. As clinical study participants, they help researchers to discover new medicines for the benefit of all patients.

This document is a summary of the study. It is written for a general audience.

Researchers need many studies to decide which medicines work the best and are the safest for the patients. For medical science to progress, a lot of people in many studies are involved all around the world. This summary only shows the results from this one study. Other studies, evaluating the same drug, may find different results.

You should not change your current treatment based on the results of this single study. If you have any questions about this study, please talk to your doctor.

1 Why was this study done?

This study was done to test a new anticancer drug in leukaemia.
The current name of the study drug is UCART19, also called "S68587".
UCART19 is made of specially modified cells, designed to kill leukaemia cells. It is a "cell-based gene therapy".

The main objectives of this study were:

- To look at the safety of UCART19.
- To find the highest tolerated dose of UCART19. This highest tolerated dose helps to find the "recommended dose" (dose that could be both safe and effective for patients).
- To find the best treatment to eliminate white blood cells (called lymphocytes) and prepare the blood to receive UCART19 cells." This is called "lymphodepletion treatment".

2 When and where did this study take place?

When was it performed?

- This study started in August 2016.
- It ended in July 2020.

Where did the study take place?

The study took place in the following countries:

Country	Number of patients
United Kingdom	11 patients
France	6 patients
United States	6 patients
Japan	2 patients

3 Who participated in the study?

Which patients were included in the study?

Patients in the study had to meet notably the following criteria:

- Be between 16 and 69 years old.
- Be diagnosed with a kind of blood cancer called "CD19 positive B-acute lymphoblastic leukaemia".
- Have leukaemia that came back after standard treatment, or
- Have leukaemia that did not respond to the standard treatment.
- For whom no other treatment could be further used.

How many patients participated in the study?

25 patients took part in the study (11 women and 14 men):

- 19 patients participated in Part 1 of the study.
- 6 patients participated in Part 2 of the study.

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How old were the patients?

The average age of the patients was 38 years. The youngest patient was 18 years old and the oldest patient was 64 years old.

4 Which treatments did patients receive?

All patients received the same study drug, called UCART19: 3 increasing dose levels were tested (DL1, DL2 and DL3). Each patient received a single dose of UCART19 by intravenous (into a vein) infusion. If needed, the doctor could propose an additional dose of UCART19.

Within one week before receiving UCART19 infusion, patients had a treatment called lymphodepletion (LD). There were 2 LD treatments: one called FCA* and one called FC*. Both were given by intravenous infusion.

**FCA: fludarabine + cyclophosphamide + alemtuzumab; FC: fludarabine + cyclophosphamide*

5 How was the study done?

The study is called an "open-label" study. It means that patients and doctors knew which treatment was given to the patient.

This study was done in 2 parts. Part 1 called "dose escalation part" followed by Part 2 called "expansion part".

- "Dose escalation" means that 3 different increasing doses of the study drug were tested.
- The "expansion" part of the study aimed to confirm the safety of the recommended dose of UCART19.

To find the highest tolerated dose of UCART19, each dose was tested one after the other in small groups of patients (3 to 7 patients).

For each dose of UCART19, the doctors checked the safety, especially certain severe medical events. These events, called "dose limiting toxicities" (DLT), could be caused by UCART19 during the first month after the venous infusion. Doctors were allowed to increase the dose of UCART19 for the next group of patients only if few of these severe medical events occurred. These events made it possible to define the highest tolerated dose.

Once the highest tolerated dose was found, the doctors defined the recommended dose of UCART19. Then, 6 patients entered Part 2 (the expansion part). These patients were treated with the recommended dose of UCART19.

Patients visited the doctors regularly. During the visits, the doctors collected information about the patients' health.

Once patients had completed the study, they were encouraged to be followed up for 15 years in a long-term follow-up study.

6 What were the side effects?

What about side effects?

Like all medicines, UCART19 can cause side effects, although not everybody gets them.
Side effects are unwanted medical events that the doctors think may be caused by the treatments in the study.
In this summary, we describe unwanted medical events thought to be caused by:

- UCART19 alone or
- UCART19 + LD treatment.

The table below shows the number of patients who had side effects.

	Number of patients (out of 25 patients)
Patients who had side effect(s)	23 patients (92%)
Patients who had serious* side effect(s)	12 patients (48%)

**See definition below*

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How many patients had serious side effects?

A side effect is considered "serious" when:

- The patient needs to be hospitalized.
- The patient's life is in danger.
- It causes permanent damage or death or,
- It may put the patient at risk and requires a medical intervention to prevent the situations listed above.

In this study, 12 patients out of 25 (48%) had serious side effects.
The serious side effects reported in at least 3 patients are described in the table below.

	Number of patients (out of 25 patients)
Symptoms caused by the release of a large amount of chemicals from cells following the drug infusion (leading to fever, vomiting, shortness of breath, headache and/or low blood pressure…)	10 patients (40%)
Decreased production of blood cells by the bone marrow (the spongy tissue inside the bones)	3 patients (12%)
Low number of cells in the blood	3 patients (12%)
Condition in which some immune cells damage body tissues or organs	3 patients (12%)

In the study, 3 patients died because of an unwanted medical event that doctors thought maybe caused by UCART19:

- One patient died of lung bleeding.
- One patient died of dysfunction of two or more organs and severe infection of the blood.
- One patient died of dysfunction of two or more organs and serious body reaction to an infection.

What were the other side effects?

The table below shows the other side effects reported in the study. Only the most common (reported in at least 3 patients) are presented.

	Number of patients (out of 25 patients)
Symptoms caused by the release of a large amount of chemicals from cells following the drug infusion (leading to fever, vomiting, shortness of breath, headache and/or low blood pressure…)	12 patients (48%)
Increase in liver enzyme called ALT	3 patients (12%)
Decrease in the number of red blood cells	3 patients (12%)
Increase in liver enzyme called AST	3 patients (12%)

7 What were the study results?

The study was completed as planned.

During the dose escalation part, 3 patients experienced dose limiting toxicity (DLT): one DLT occurred with each of the 3 dose levels (DL1, DL2, DL3). DLTs are severe medical events that doctors checked for in order to decide if they could increase the dose of UCART19 or not.

The highest tolerated dose found during Part 1 was UCART19 dose level DL3. Based on both safety and antitumoral activity, the recommended dose chosen was dose level DL2.

The lymphodepletion treatment chosen was the FCA treatment as it seemed to be more effective than FC.

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8 How has this study helped patients and researchers?

This study helped researchers in their understanding of UCART19 use for this kind of cancer. By participating in this study, patient had close medical follow-up with experts in cancer.

9 Are there plans for further studies?

The company decided to stop the research on S68587 (a UCART19 Product) in this kind of cancer.

Additional research with a similar drug is continuing for another kind of blood cancer called « non-Hodgkin lymphoma ». The company and its Partner are reviewing their development strategy in acute lymphoblastic leukaemia.

10 Further information

What is the identification number of the clinical study?

- Protocol Number: CL1-68587-002
- EudraCT Number: 2016-000296-24

Who did the study?

The company organizing and funding the research, called the “Sponsor”, is the Institut de Recherches Internationales Servier based in Suresnes, France.

This study used UCART19 which is an anti-CD-19 allogeneic CAR-T product developed based on an exclusive licence granted by Cellectis to Servier. UCART19 uses Cellectis’ technologies, including TALEN® gene-editing technologies.

How can you contact the sponsor?

Contact us on the Servier’s website (www.servier.com).

Where can you learn more about this study?

- The scientific summary is also available on the Servier Clinical Trial Data website. (https://clinicaltrials.servier.com/)
- In this document, we translated medical terms into lay terms. You can find the corresponding medical terms in the Servier glossary on the Servier Clinical Trial Data website.

In accordance with the recommendations of the Cancer Plan III (Measure 5.4), this document was submitted for review and guidance to the Clinical Cancer Research Patients Committee of La Ligue Nationale contre le Cancer.