NOVARTIS

Clinical Trial Results Summary

A clinical trial to learn more about the safety of CTL019 given with ibrutinib in people with diffuse large B-cell lymphoma (DLBCL)

Clinical trial protocol number: CCTL019L12101C

Thank you!

Thank you to the participants who took part in the clinical trial for the drug **CTL019**, also known as **tisagenlecleucel**. All of the participants helped the researchers learn more about how **CTL019** given with **ibrutinib** works in people with **diffuse large B-cell lymphoma (DLBCL).**

Novartis sponsored this clinical trial and believes it is important to share what was learned from the results of this trial with the participants and the public.

? **If you were a participant and have any questions about the results, please talk to the doctor or staff at the trial site.**

This summary only shows the results of a single clinical trial. Other clinical trials may have different findings.

Why was the research needed?

Researchers are looking for a better way to treat **diffuse large B-cell lymphoma (DLBCL)** that is **relapsed** or **refractory**. At the time when this study started, most patients with relapsed or refractory DLBCL would die within a year of being diagnosed. DLBCL is the most common and fast-growing type of non-Hodgkin lymphoma, which is a type of blood cancer. In DLBCL, white blood cells called B-cells grow too quickly and can form tumors throughout the body. **B-cells** are part of the body's immune system and make antibodies (proteins) to help fight infections.

Relapsed means DLBCL came back after previous treatment. **Refractory** means DLBCL did not respond to previous treatment.

CTL019 is a cancer treatment approved in some countries to treat people with certain types of B-cell cancers, including DLBCL that is relapsed or refractory. CTL019 is a type of chimeric antigen receptor (CAR) T-cell therapy. **CAR T-cell therapy** is a cancer treatment that uses a person's own **T-cells** (another type of white blood cell) to find and kill cancer cells. It has not been approved to be given with certain other cancer treatments, such as ibrutinib.

Ibrutinib is a drug approved in many countries to treat different types of blood cancers, such as chronic lymphocytic leukemia. Ibrutinib is not approved to treat DLBCL. Researchers wanted to know if giving CTL019 with ibrutinib could help CTL019 stay in the blood longer and lessen the severity of certain side effects.

Trial purpose

The main purpose of this trial was to learn about the safety of CTL019 given with ibrutinib in people with relapsed or refractory.

The main questions the researchers wanted to answer in this trial were:

- What medical problems did the participants have during the trial?
- How many participants had to pause taking ibrutinib or lower its dose?

How long was this trial?

The trial started in June 2019 and ended in November 2021. This trial was designed so that each participant could take part for up to about 2 years.

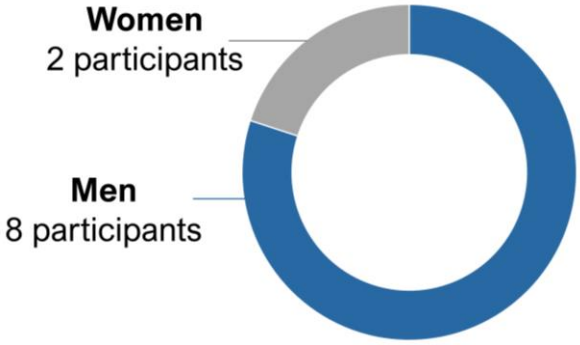
However, Novartis decided to end this trial early because new treatments for DLBCL became available. The decision to end the trial was not related to safety. Because it ended early, each participant had the option to join another long-term follow up trial to check their general health and safety for up to 15 years after they received CTL019.

When the trial ended, the researchers collected information on the trial treatments and created a report of the trial results. This summary is based on that report.

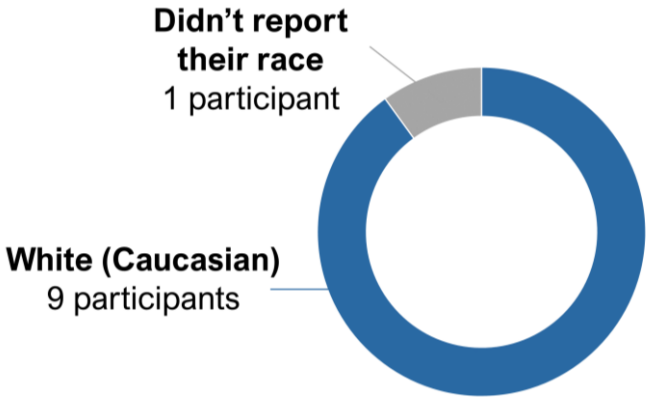
Who was in this trial?

10 participants with **relapsed or refractory DLBCL** were in this trial. Participants' ages ranged from 32 to 76 years old. Their average age was 61 years old.

Participant gender



Participant race



The participants could take part in this trial if they had DLBCL that was relapsed or refractory and:

- Their tumor size could be measured
- No other type of blood cancer
- Had not taken ibrutinib within 30 days
- Had never received any other gene or T-cell therapy

Participants took part at 2 trial sites in the United States.

What treatments did the participants take?

The treatments in this trial were:

CTL019, also known as tisagenlecleucel, is a type of CAR T-cell therapy.
To prepare CTL019, trial doctors:

1. Take T-cells from a participant's blood
2. Change (genetically modify) their T-cells in the lab to help the T-cells find and kill cancerous B-cells
3. Give the changed T-cells (CTL019) to the participant through a vein (intravenous or IV infusion)

Ibrutinib, which is a drug approved in many countries to treat different types of blood cancers by blocking proteins that help cancer cells copy themselves. It was taken by mouth as tablets as 560 milligrams (mg) once a day.

In this trial, all participants and clinical trial team knew what treatment each participant received. All participants received CTL019 and ibrutinib.

What happened during this trial?

Up to 4 weeks before treatment with ibrutinib

During screening

Trial doctors checked participants' health and DLBCL to make sure they could be in this clinical trial.

10 participants took part in this trial.

One dose of CTL019

Started taking ibrutinib

During treatment

The trial enrolled participants into 2 groups at the same time:

- **Group 1 (4 participants):** Participants started taking ibrutinib **28 days before doctors took their T-cells** to make CTL019. They took ibrutinib for 8 to 10 weeks before receiving CTL019 and kept taking afterwards for up to 65 weeks total.
- **Group 2 (6 participants):** Participants started taking ibrutinib **after doctors took their T-cells** to make CTL019. They took ibrutinib for 4 to 6 weeks before receiving CTL019 and kept taking afterwards for up to 65 weeks total.

The trial doctors could stop or lower a participant's dose of ibrutinib if they had certain side effects or their DLBCL either got worse or completely disappeared.

After the first 2 participants in each group received CTL019 and took ibrutinib for a few weeks, trial doctors checked for any safety concerns before having the rest of the participants receive CTL019 and ibrutinib.

The participants could also take certain medicines to treat possible side effects from the CTL019 infusion. Trial doctors checked the participants' DLBCL and general health throughout the trial.

Up to 24 months after treatment with CTL019

Follow-up after treatment with CTL019

Participants returned to their trial site 17 times for researchers to check their health, survival, and continued treatment with ibrutinib for up to 65 weeks total:

- 8 times during the first month after receiving CTL019
- 7 times during the rest of the first year after receiving CTL019
- 2 times during the second year after receiving CTL019

What were the main results of this trial?

What medical problems did the participants have during the trial?

The researchers found no new safety concerns for CTL019 given with ibrutinib in this trial. The safety results for participants who started taking ibrutinib before doctors took their T-cells (Group 1) were about the same as those who started taking it after doctors took their T-cells (Group 2).

Medical problems that happen in clinical trials are called "**adverse events**".

A lot of research is needed to know whether a drug causes an adverse event. So, when new drugs are being studied, researchers keep track of all adverse events the participants have, whether or not they are thought to be caused by the trial treatment.

This section is a summary of the adverse events that happened during this trial. The websites listed at the end of this summary have more information about the adverse events that happened in this trial.

An **adverse event** is any sign or symptom that participants have during a trial. An adverse event is considered "**serious**" when it is life-threatening, causes lasting problems, or the participant needs hospital care. These problems may or may not be caused by the trial treatment.

How many participants had adverse events?

The number of participants in the 2 groups who had adverse events:

	Group 1 Started ibrutinib **before** T-cells taken **4 participants**	Group 2 Started ibrutinib **after** T-cells taken **6 participants**
Participants who had at least 1 adverse event	4 of 4 100%	6 of 6 100%
Participants who had at least 1 serious adverse event	2 of 4 50%	3 of 6 50%
Participants who left the trial due to an adverse event	1 of 4 25%	0 of 6 0%
Deaths due to DLBCL getting worse that were reported as a serious adverse event	0 of 4 0%	1 of 6 17%

What were the serious adverse events?

5 of 10 participants (50%) had at least one serious adverse event. The most common serious adverse event, which was reported by 2 participants (20%), was **back pain**.

One participant died due to DLBCL getting worse, and the trial staff reported it as a serious adverse event.

What were the most common non-serious adverse events?

10 of 10 participants (100%) had at least one adverse event that was not considered serious.

Most common adverse events, which happened in at least 6 of 10 participants (60% or more)

	Group 1 Started ibrutinib **before** T-cells taken **4 participants**	**Group 2** Started ibrutinib **after** T-cells taken **6 participants**
Low levels of white blood cells White blood cell count decreased	2 of 4 50%	6 of 6 100%
Low levels of a type of white blood cell Neutrophil count decreased	1 of 4 25%	6 of 6 100%
High blood sugar Hyperglycemia	1 of 4 25%	5 of 6 83%
Low level of albumin, which is a blood protein Hypoalbuminemia	1 of 4 25%	5 of 6 83%
Low level of red blood cells Anemia	1 of 4 25%	5 of 6 83%

How many participants had to pause taking ibrutinib or lower their dose?

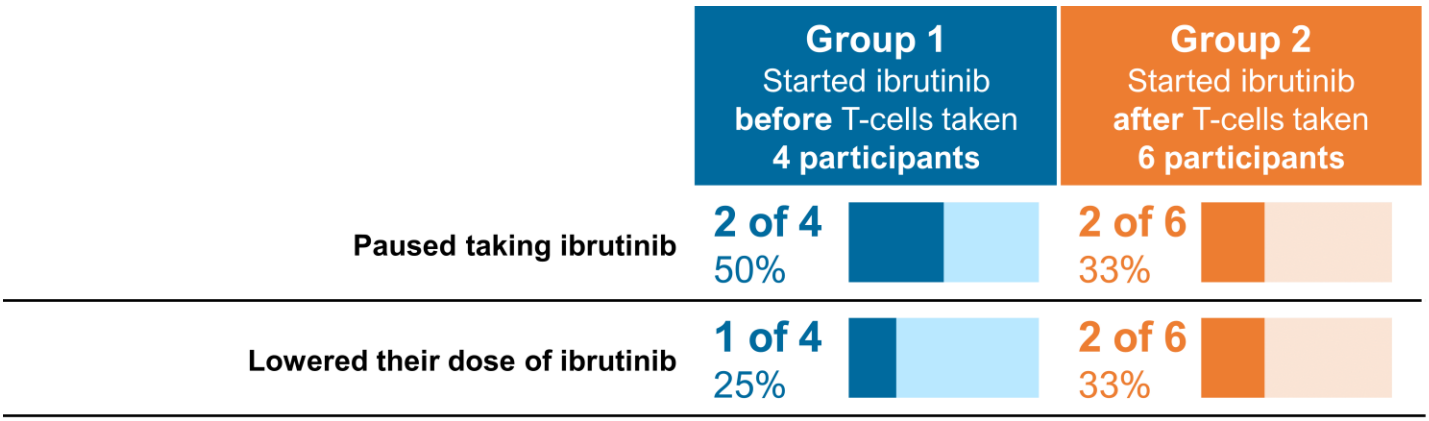
Up to half of the participants in each group had to pause taking ibrutinib. At least one participant in each group had to lower their dose of ibrutinib. The main reason was because of adverse events. The researchers found that the results were about the same for both groups.

The researchers learned this by keeping track of how many participants in each group had to change their dose of ibrutinib, which included to:

- Pause taking ibrutinib for a period of time (dose interruption)
- Lower their dose of ibrutinib by taking a smaller amount or taking it less often (dose reduction)

The main reason the participants paused taking ibrutinib or lowered their dose was because of adverse events, including slow heart rate and an infection.

Participants who paused taking ibrutinib or lowered their dose



What were the other results of this trial?

The researchers also kept track of participants who died due to any cause as part of the follow-up after treatment with CTL019. There were 4 participants (40%) who died due to DLBCL getting worse during the follow-up period. This is consistent with past research that about 60% of people with relapsed or refractory DLBCL who take CTL019 do not respond to it or their cancer gets worse.

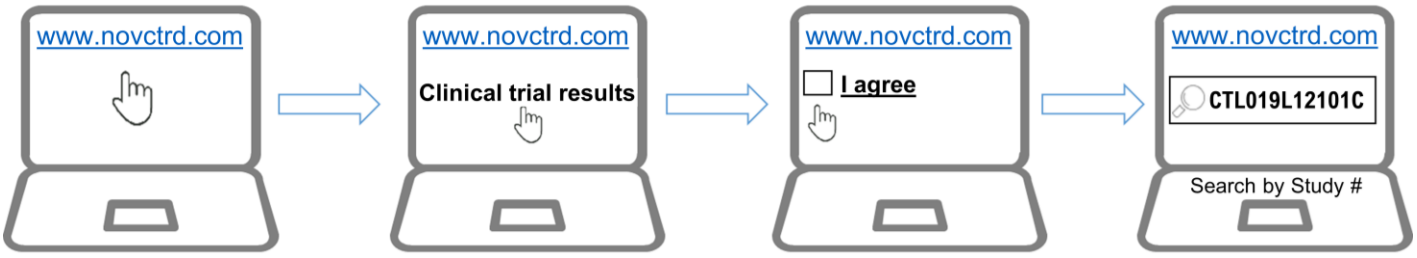
How has this trial helped?

The researchers found no safety concerns for CTL019 given with ibrutinib in this trial. The safety results for participants who started taking ibrutinib before doctors took their T-cells were about the same as those who started taking it after doctors took their T-cells.

Where can I learn more about this trial?

More information about the results and adverse events in this trial can be found in the scientific summary of the results available on the Novartis Clinical Trial Results website (www.novctrd.com).

Follow these steps to find the scientific summary:



You can find more information about this trial on this website:

- www.clinicaltrials.gov. Use the NCT identifier NCT03876028 in the search field.

Full clinical trial title: A phase Ib, multicenter study to determine the safety and tolerability of tisagenlecleucel in combination with ibrutinib in adult patients with relapsed and/or refractory diffuse large B-cell lymphoma

Thank you

Thank you to all trial participants. Clinical trial participants belong to a large community of people who take part in clinical research around the world. They help researchers answer important health questions and test new medical treatments for patients.

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Novartis is a global healthcare company based in Switzerland that provides solutions to address the evolving needs of patients worldwide.

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