NOVARTIS

Clinical Trial Results Summary

A clinical trial to learn about the effects and safety of BLZ945 in people with amyotrophic lateral sclerosis (ALS)

Thank you!

Thank you to the participants who took part in the clinical trial for **ALS**, also called Lou Gehrig's disease. Every participant helped the researchers learn more about the trial drug **BLZ945**, also called sotuletinib.

Novartis sponsored this trial and believes it is important to share what was learned from the results of this trial with the participants and the public. We hope this helps the participants understand their important role in medical research.

Trial information

Trial number: CBLZ945C12201

Novartis drug studied: **BLZ945**, also called sotuletinib

Sponsor: Novartis

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 results.

What was the main purpose of this trial?

The purpose of this trial was to learn about the effects and safety of **BLZ945** in people with amyotrophic lateral sclerosis, or ALS.

ALS is a long-term nervous system condition that affects nerve cells in the brain and spinal cord. In ALS, nerve cells called motor neurons become damaged, weak, and die over time. **Motor neurons** control voluntary muscle movements and breathing.

Early ALS symptoms often include muscle twitching, arm or leg weakness, trouble swallowing, or slurred speech. Symptoms get worse over time and affect the ability to move, speak, eat, and breathe.

Because of the damage to motor neurons, people with ALS often have **inflammation** in the brain. People with ALS may also have more inflamed microglia in the brain. **Microglia** are the main type of immune cell in the brain. When microglia are activated, they become inflamed and may play a role in ALS.

What is inflammation?

Inflammation is one of the ways the immune system repairs damage and protects the body from disease and infection. However, too much inflammation can be harmful.

BLZ945, is a trial drug designed to lower the number of inflamed microglia in the brain. Researchers think lowering the number of inflamed microglia may lower inflammation in the brain and slow down symptoms of ALS over time.

The trial's purpose was to answer these main questions:

- Did different dose levels of BLZ945 lower the amount of inflamed microglia in each participant's brain?
- How many participants had certain safety concerns?
- Did walls in the esophagus or heart get thicker in participants after taking BLZ945?
- What medical problems, also called adverse events, happened during this trial?
  - ↳ An **adverse event** is any sign or symptom that participants have during a trial. Adverse events **may** or **may not** be caused by treatments in the trial.

How long was this trial?

The trial began in December 2019 and ended in February 2024.

This trial was designed to have 2 parts:

- **Part 1**: Participants took **BLZ945** for 4 days
- **Part 2**: Participants took **BLZ945** for up to 3 months

In March 2024, the trial ended early because the sponsor decided to stop all research on **BLZ945** in people with ALS. The sponsor reviewed the available data and concluded that the possible benefits of **BLZ945** in people with ALS no longer outweighed the possible risks.

Who was in this trial?

In **Part 1**, 16 participants with ALS received treatment in this trial – 9 men and 7 women. Participants' ages ranged from 33 to 76 years.

The number of participants by race is shown below.

Race

15 White	1 Unknown

In **Part 2**, 12 participants with ALS received treatment in this trial – 9 men and 3 women. Participants' ages ranged from 32 to 74 years.

The number of participants by race is shown below.

Race

12 White

The participants could take part in this trial if they:

- Had ALS symptoms for less than 4 years
- Were being treated for ALS and had not changed their treatment plan in the last month
- Did not have certain heart conditions

28 participants from 3 countries received treatment.

- Finland | 8 participants
- Sweden | 12 participants
- United States | 8 participants

What treatments did the participants receive?

The treatment in this trial was:

BLZ945, which participants took by mouth as a capsule.

This trial looked at 4 dose levels of **BLZ945**:

- 300 milligrams (mg)
- 600 mg
- 800 mg
- 1,200 mg

The participants took their treatment either once a day or once a week.

All participants could continue taking certain medicines for ALS during the trial.

For **Part 1**, the trial staff and sponsor assigned participants to a treatment dose level. The participants took **BLZ945** once a day.

For **Part 2**, researchers used a computer to randomly assign participants to take **BLZ945** on 1 of 2 treatment schedules:

- **Schedule 1**: Once a day for the first 4 days of every 2-week cycle. A **cycle** is a treatment period that is repeated.
- **Schedule 2**: Once a week

The participants, researchers, and trial staff knew what treatment each participant took. All participants took **BLZ945**.

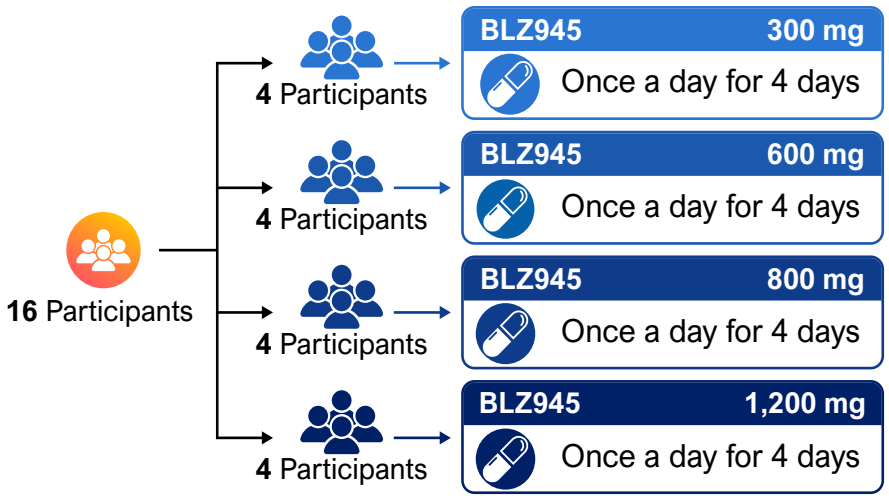
What happened during this trial?

Before treatment — Up to 6 weeks

The trial staff checked to make sure the participants could be in this trial.

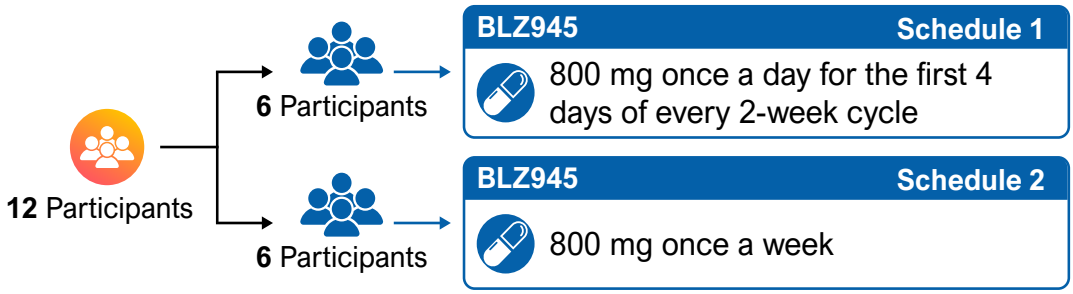
During treatment — Part 1 (4 days) Part 2 (Up to 9 months)

Part 1: The graphic below shows how many participants were assigned to each dose level.



In Part 1, participants taking 300mg **BLZ945** started treatment first. If there were no safety concerns, the next group started treatment with a higher dose.

Part 2: Certain results from Part 1 suggested that giving **BLZ945** for longer might have a larger effect. Therefore the researchers changed how long to give **BLZ945** in Part 2. The graphic below shows how many participants were assigned to each treatment schedule.



BLZ945 was taken for a total of 3 months. If participants completed the first 3 months of treatment, they could choose to continue treatment for another 6 months.

After treatment — Up to 1 year

Trial staff checked participants' general health and for any medical problems for up to 1 month after their last dose of treatment.

Trial staff called participants in Part 2 who continued treatment or had safety concerns, to check on their health every 3 months for about a year.

Trial staff checked the participants' general health throughout the trial.

What were the main results of this trial?

Did different doses of BLZ945 lower the amount of inflamed microglia in each participant's brain?

Part 1: On average, the amount of inflamed microglia was:

- Lower after taking 600 mg or 1200 mg **BLZ945**
- About the same after taking 300 mg **BLZ945**
- Slightly higher after taking 800 mg **BLZ945**

Because there were too few results, the researchers could not conclude if the higher result was meaningful.

Part 2, Schedule 1: The amount of inflamed microglia was lower after taking 800 mg of **BLZ945**. However, there were too few results for researchers to conclude if the result was meaningful.

To learn this, researchers looked at PET scan images of participants' brains before and after taking **BLZ945**. Researchers measured the amount of inflamed microglia cells on the PET scan images and compared it from before and after taking **BLZ945**.

If the amount of inflamed microglia goes **down**, it may be a sign of **less** inflammation in the brain.

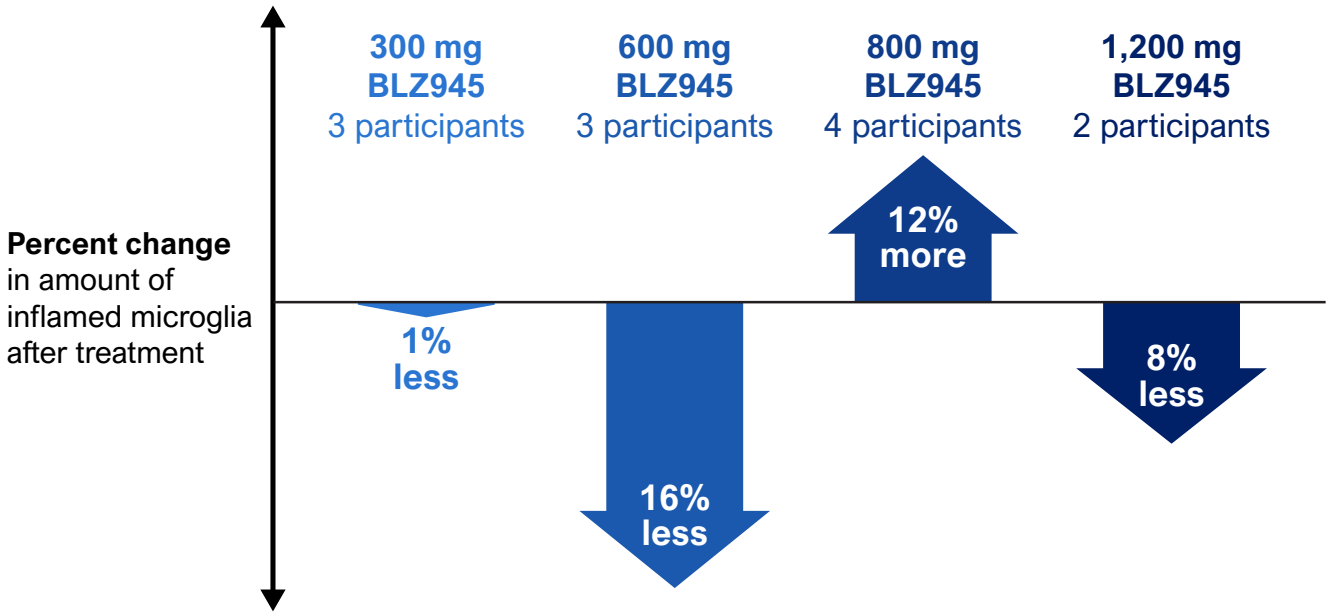
Trial staff took PET scans of participants in Part 1, and participants assigned Schedule 1 in Part 2. In Schedule 1, participants took **BLZ945** once a day for the first 4 days of every 2-week cycle for 3 months.

What is PET?

PET (positron emission tomography) is an imaging test that can help doctors find specific cells and inflammation. In this trial, the participants had PET scans to measure the amount of inflamed microglia cells.

Part 1: Change in the amount of inflamed microglia in the brain after 4 days of treatment

The graph below shows the average percent change in the amount of inflamed microglia cells on participants' PET scan images. The graph below includes only those participants who had PET scan results available.



Less inflamed microglia may be a sign of **less** inflammation in the brain.

Because there were too few results, the researchers could not conclude if the higher result for 800 mg **BLZ945** was meaningful.

In **Part 2**, PET scans from 1 participant taking **BLZ945** on Schedule 1 showed less inflamed microglia after 3 months of treatment. However, because there were too few results, researchers could not conclude if this result was meaningful.

Part 2: Did the esophagus or heart get thicker in participants after taking BLZ945?

Overall, the researchers did not find any meaningful changes in the thickness of the esophagus and heart.

Past research on **BLZ945** suggested it could cause proteins and cells to build up in certain parts of the body. This buildup was seen in the eyelids, heart, and esophagus. The **esophagus** is the tube that connects the throat to the stomach. The buildup of proteins and cells can cause organs to thicken. The researchers were concerned that this could affect how well the organs work.

To learn if participants in Part 2 had changes in the thickness of their esophagus or heart, each participant had these tests:

- **CT scans**, which is an imaging test that creates detailed pictures of the esophagus
- **Heart ultrasounds**, which is an imaging test that looks at the heart while it pumps and rests to check how well the heart works

Part 2: How many participants had certain safety concerns?

4 of 12 participants had certain safety concerns, such as swelling in or around the eyes, 3 months after starting treatment.

Trial doctors looked for certain safety concerns that could happen from proteins and cells building up in the tissues, including:

- Swelling in or around the eyes
- Heart problems, such as more trouble breathing, chest pain, or fainting
- More trouble swallowing

Part 2: Number of participants who had certain safety concerns

The table below shows the number of participants who had certain safety concerns during their first 3 months of treatment.

	Schedule 1 800 mg BLZ945 in 2-week cycles 6 participants	**Schedule 2 800 mg BLZ945 once a week** 6 participants
Participants with certain safety concerns	**2 of 6** 33%	**2 of 6** 33%

What medical problems, also called adverse events, happened during this trial?

Trial doctors keep track of all medical problems, also called **adverse events**, that happen in trials. They track adverse events even if they think the adverse events are not related to the trial treatments.

Many trials are needed to know if a drug or treatment causes an adverse event.

This section is a summary of the adverse events that happened from the start of treatment until 1 month after the last treatment.

An **adverse event** is:

- Any **sign or symptom** that the participants have during a trial
- Considered **serious** when it is life-threatening, causes lasting problems, the participant needs hospital care, or results in death

Adverse events **may** or **may not** be caused by treatments in the trial.

In **Part 1**, most of the participants (12 of 16) had adverse events. 1 participant had an adverse event that was considered serious. No participants left the trial due to an adverse event. No participants died.

In **Part 2**, all 12 participants had adverse events. 4 participants had adverse events that were considered serious. 1 participant left the trial due to an adverse event. 2 participants died.

There were some safety concerns for **BLZ945** in this trial. The sponsor decided to stop all research on **BLZ945** in people with ALS because the possible benefits no longer outweighed the possible risks.

Part 1: How many participants had adverse events?

	300 mg BLZ945 4 participants	600 mg BLZ945 4 participants	800 mg BLZ945 4 participants	1,200 mg BLZ945 4 participants
Had at least 1 **serious adverse event**	0 of 4 0%	0 of 4 0%	0 of 4 0%	1 of 4 25%
Had at least 1 **other adverse event**	2 of 4 50%	2 of 4 50%	4 of 4 100%	4 of 4 100%
Left the trial due to an adverse event	0 of 4 0%	0 of 4 0%	0 of 4 0%	0 of 4 0%
Died	0 of 4 0%	0 of 4 0%	0 of 4 0%	0 of 4 0%

Part 2: How many participants had adverse events?

	Schedule 1 800 mg BLZ945 in 2-week cycles 6 participants	Schedule 2 800 mg BLZ945 once a week 6 participants
Had at least 1 **serious adverse event**	0 of 6 0%	4 of 6 67%
Had at least 1 **other adverse event**	6 of 6 100%	6 of 6 100%
Left the trial due to an adverse event	0 of 6 0%	1 of 6 17%
Died	0 of 6 0%	2 of 6 33%

What serious adverse events did the participants have?

In **Part 1**, 1 participant had serious adverse events. No participants died.

The serious adverse event that happened in 1 participant who took 1,200 mg **BLZ945** was:

- **Low sodium levels in the blood** | Hyponatremia

In **Part 2**, 4 participants had serious adverse events. 2 participants who were assigned to Schedule 2 died.

The table below shows the serious adverse events that happened in **Part 2**.

	Schedule 1 800 mg BLZ945 in 2-week cycles 6 participants	Schedule 2 800 mg BLZ945 once a week 6 participants
Lungs can't get enough oxygen into the blood Respiratory failure	0 of 6 0%	2 of 6 33%
Lung infection from breathing food or liquid into the lungs Pneumonia aspiration	0 of 6 0%	2 of 6 33%
Lung infection Pneumonia	0 of 6 0%	1 of 6 17%
Sign of liver damage Transaminases increased	0 of 6 0%	1 of 6 17%

What other adverse events did the participants have?

In **Part 1**, 12 participants had other adverse events.

The table below shows the other adverse events that happened in **3 or more** participants across all dose levels. Additional adverse events happened in fewer participants.

	300 mg BLZ945 4 participants	600 mg BLZ945 4 participants	800 mg BLZ945 4 participants	1,200 mg BLZ945 4 participants
Feeling dizzy Dizziness	2 of 4 50%	0 of 4 0%	2 of 4 50%	1 of 4 25%
Headache	2 of 4 50%	0 of 4 0%	0 of 4 0%	3 of 4 75%
Feeling sick to the stomach Nausea	1 of 4 25%	0 of 4 0%	1 of 4 25%	3 of 4 75%
Frequent, loose, or watery stool Diarrhea	1 of 4 25%	1 of 4 25%	1 of 4 25%	0 of 4 0%
Feeling weak and tired Fatigue	1 of 4 25%	0 of 4 0%	0 of 4 0%	2 of 4 50%
Throwing up Vomiting	1 of 4 25%	0 of 4 0%	1 of 4 25%	1 of 4 25%

In **Part 2**, 12 participants had other adverse events.

The table below shows the other adverse events that happened in **3 or more** participants across both schedules. Additional adverse events happened in fewer participants.

	Schedule 1 800 mg BLZ945 in 2-week cycles 6 participants	Schedule 2 800 mg BLZ945 once a week 6 participants
Feeling weak and tired Fatigue	3 of 6 50%	2 of 6 33%
Headache	3 of 6 50%	2 of 6 33%
Fall	2 of 6 33%	2 of 6 33%
Feeling sick to the stomach Nausea	3 of 6 50%	1 of 6 17%
Possible sign of liver damage Aspartate aminotransferase increased	1 of 6 17%	2 of 6 33%

What was learned from this trial?

Researchers learned about the effects and safety of **BLZ945** in people with ALS. The trial ended early because the possible benefits of **BLZ945** in people with ALS no longer outweighed the possible risks.

The researchers concluded in **Part 1**, on average, the amount of inflamed microglia was:

- Lower after taking 600 mg or 1200 mg of **BLZ945**.
- About the same after taking 300 mg of **BLZ945**.
- Slightly higher after taking 800 mg of **BLZ945**. Because there were too few results, the researchers could not conclude if the higher result was meaningful.

The researchers concluded in **Part 2**:

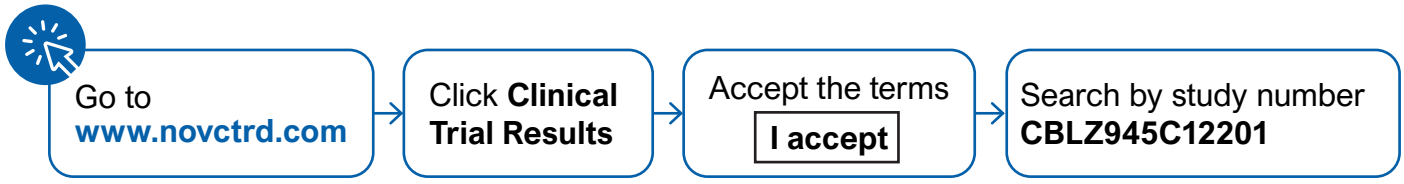
- The amount of inflamed microglia was lower after taking 800 mg of **BLZ945** in Schedule 1. However, there were too few results for researchers to conclude if the result was meaningful.
- Overall, the researchers did not find any meaningful changes seen in the thickness of the esophagus and heart.
- Some participants in Part 2 had certain safety concerns while taking **BLZ945**.

When this summary was written, the sponsor had no plans for future trials of **BLZ945** in people with ALS.

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:



For more information about this trial, go to any of these websites:

- **clinicaltrials.gov** – search using the number **NCT04066244**
- **clinicaltrialsregister.eu/ctr-search/search** – search using the number **2019-000826-22**

Other trials of **BLZ945** may appear on the public websites above. When there, search for **BLZ945** or sotuletinib.

Full clinical trial title: An open-label, adaptive design study in patients with amyotrophic lateral sclerosis (ALS) to characterize safety, tolerability and brain microglia response, as measured by TSPO binding, following multiple doses of BLZ945 using positron emission tomography (PET) with the radioligand[11C]-PBR28

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