NOVARTIS

The effects and safety of CDZ173 for adults and young adults with APDS

Thank you!

Thank you to the participants who took part in the clinical trial for the trial drug **CDZ173**, also called leniolisib. Every participant helped the researchers learn more about CDZ173 for people with **APDS**, which stands for **activated phosphoinositide 3-kinase delta syndrome**. APDS is also known as PASLI or p110δ-activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency.

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: CCDZ173X2201
Drug studied: CDZ173
Sponsor: Novartis

What was the main purpose of this trial?

The purpose was to learn about the safety and effects of CDZ173 in people with APDS.

APDS is a genetic condition that leads to a weakened immune system. In APDS, a protein called PI3K delta has too high of an activity level.

PI3K delta usually controls how white blood cells in the immune system develop. When PI3K delta is overactive, white blood cells don't work well to protect the body from infection. It can also cause white blood cells to build up in lymph nodes, which leads to swelling.

Lymph nodes are tiny, bean-shaped organs that filter out infections. They also contain white blood cells to fight infection.

For this trial, researchers looked at a type of white blood cell called **B cells**.

CDZ173 is a trial drug designed to lower the activity of PI3K delta.

This trial had 2 parts. Each looked at the safety of CDZ173 and:

- **Part 1** focused on how different doses of CDZ173 lowered the activity of PI3K delta in participants with APDS. This helped researchers decide which dose amount to use in Part 2.
- **Part 2** focused on the effects of CDZ173 in participants with APDS.

The main questions Part 1 of this trial was designed to answer:

- Which dose of CDZ173 lowered the activity of PI3K delta the most?
- What medical problems did the participants have during Part 1?
  Keeping track of the medical problems helped to learn about the safety of CDZ173.

Part 1 main results: The high dose of CDZ173 lowered the activity of PI3K delta the most and for the longest time. Because of this, the researchers chose to use the high dose of CDZ173 in Part 2. The researchers concluded there were no safety concerns for CDZ173 during Part 1.

The main questions Part 2 of this trial was designed to answer:

- Did CDZ173 shrink the participants' most swollen lymph nodes?
- Did CDZ173 raise the number of certain B cells?
- What medical problems did the participants have during Part 2?

Part 2 main results: The most swollen lymph nodes shrank more on average in participants who took CDZ173 compared to those who took the placebo. In some of the participants, the number of certain B cells went up more in those who took CDZ173. The researchers concluded these were meaningful differences. The researchers also concluded there were no safety concerns for CDZ173 during Part 2.

How long was this trial?

The trial began in August 2015 and ended in August 2021. It was planned for the participants to be in Part 1 or Part 2 for about 6 months.

Who was in this trial?

All participants in this trial had APDS. They participated in either Part 1 or Part 2:

Part 1

6 participants – 4 males and 2 females. They were 16 to 31 years old. Their average age was 22. All 6 participants reported their race as White (Caucasian).

Part 2

31 participants – 15 males and 16 females. They were 12 to 54 years old. Their average age was 24.

Participants reported their race as:

- White (Caucasian) – 25 participants
- Asian – 2 participants
- Black – 2 participants
- More than one race – 2 participants

All 31 participants had at least one swollen lymph node that could be seen using imaging tests.

This trial took place in Belarus, Czech Republic, Germany, Ireland, Italy, the Netherlands, Russian Federation, the United Kingdom, and the United States.

Visit **novctrd.com** for more information about:

- Who could and could not be in this trial
- Reasons why the participants did not complete the trial

Use trial number **CCDZ173X2201** to find the scientific summary.

What trial treatments did the participants take?

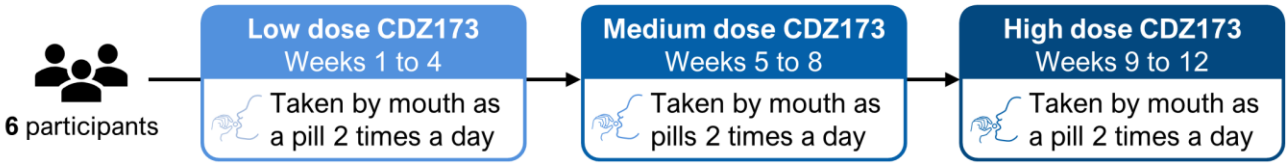
The participants took different trial treatments in Part 1 and Part 2.

Part 1 trial treatments

Every participant took each of these treatments as pills:

- **Low dose CDZ173** – 10 milligrams (mg)
- **Medium dose CDZ173** – 30 mg
- **High dose CDZ173** – 70 mg

The graphic below shows how long and how often participants took each treatment.



Each participant started with the low dose. The trial doctor checked for safety concerns while participants took each dose. After a participant finished 4 weeks of a dose and had no safety concerns, they started the next higher dose. Everyone knew which treatment the participants took.

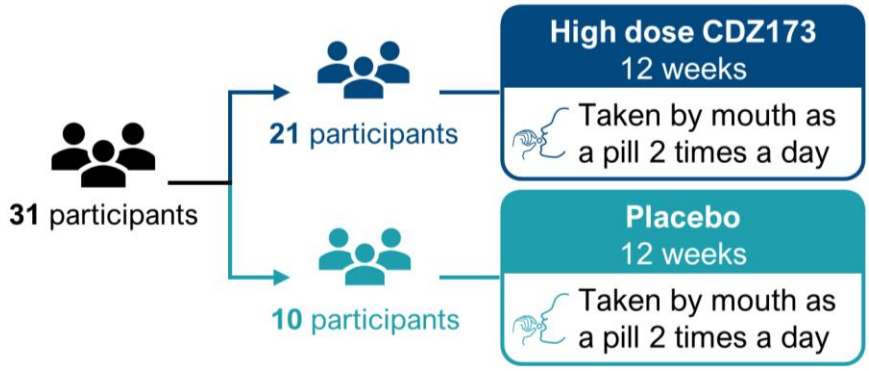
Part 2 trial treatments

Every participant took one of these treatments as a pill:

- **CDZ173 high dose** – 70 mg
- **Placebo** – looks like the trial drug but has no trial drug in it. Using a placebo helps researchers better understand the actual effects of a trial drug.

A computer program was used to randomly assign the treatment each participant took. Using a computer program to assign the treatments helped make sure the researchers compared the results as fairly as possible.

The participants, sponsor staff, and trial staff did not know what treatment each participant took during Part 2. Some trials are done this way because knowing what treatment participants take can influence some of the results. Not knowing what treatment participants take helps make sure the results are looked at fairly. The graphic below shows how many participants were assigned each treatment.



What were the main results of this trial?

This is a summary of the overall results of this trial. Individual results from each participant may be different and are not included in this summary.

Researchers need many trials to learn if a drug or other treatment is safe and works well. Other trials may provide new information or different results.

Always talk to a doctor before making any changes to your health care.

Part 1: Which dose of CDZ173 lowered the activity of PI3K delta the most?

The high dose of CDZ173 lowered the activity of PI3K delta the most and for the longest time. Because of this, the researchers chose to use the high dose of CDZ173 in Part 2.

The trial staff took blood samples from participants before they started CDZ173 and at different times after the start of each dose level. The staff checked the blood samples for:

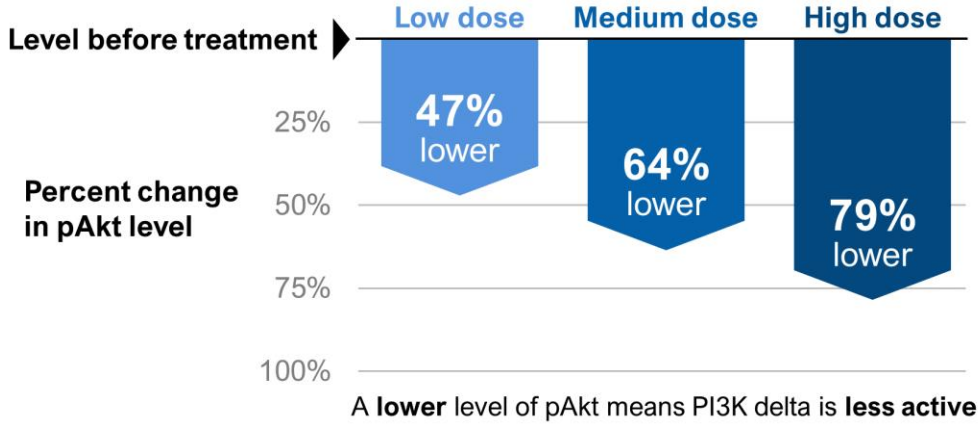
- How much CDZ173 got into the blood
- A protein called pAkt, which PI3K delta makes when it's active. **A lowered level of pAkt means PI3K delta is less active.**

The researchers found that the amount of CDZ173 in the participant's blood went up as the dose went up.

The researchers also looked at the levels of pAkt to find out how much the activity of PI3K delta changed after each dose level. The high dose of CDZ173 lowered the activity of PI3K delta the most and for the longest time.

Average change in pAkt

The graph below shows the average change in the level of pAkt after receiving each dose of CDZ173 for 4 weeks. The researchers compared the pAkt levels from before treatment to after treatment at each dose level.



Trial staff ran 2 tests on the blood samples to confirm the changes in pAkt and PI3K delta. As expected, the results of both tests were about the same.

The trial doctors, researchers, and country health authorities reviewed these results. They agreed to use the high dose in Part 2.

Part 2: Did CDZ173 shrink the participants' most swollen lymph nodes?

Yes, on average, the most swollen lymph nodes shrank more in participants who took CDZ173 than those who took the placebo after 12 weeks. The researchers concluded this was a meaningful difference.

To find this out, the trial doctors took images of each participant's lymph nodes with either:

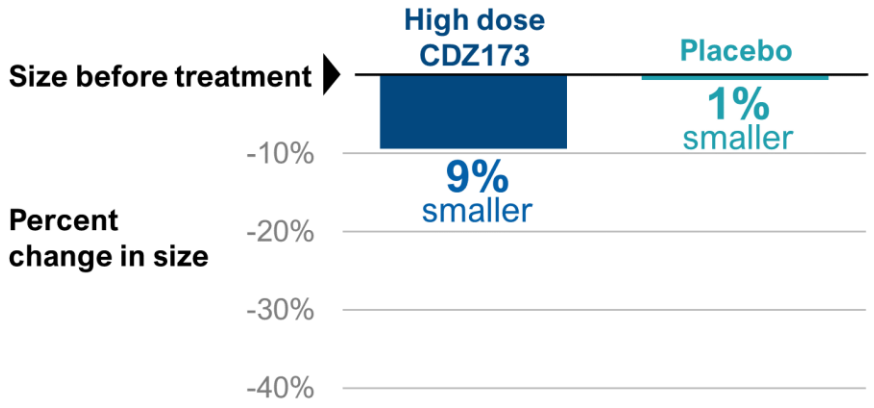
- CT or Computed Tomography scans
- MRI or Magnetic Resonance Imaging scans

The researchers compared the size of the participants' most swollen lymph nodes from before treatment to after treatment.

The most swollen lymph nodes shrank more in participants who took CDZ173 than those who took the placebo. The researchers concluded this was a meaningful difference.

Change in the size of the most swollen lymph nodes

The graph below shows the average change in the size of the participants' most swollen lymph nodes after 12 weeks of treatment.



Part 2: Did CDZ173 raise the number of certain B cells?

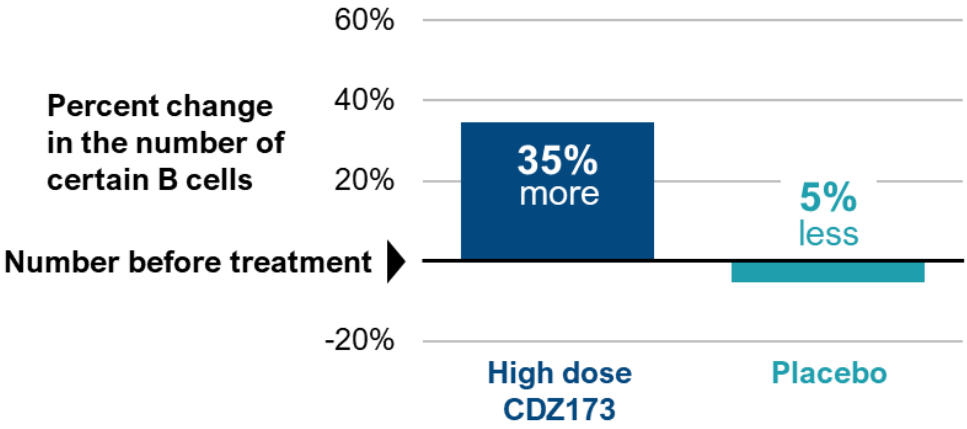
Yes, in some of the participants the number went up more in those who took CDZ173 than those who took the placebo after 12 weeks. The researchers concluded this was a meaningful difference.

To find this out, the trial staff looked at the blood samples of participants who had a low number of certain B cells. **B cells** are a type of white blood cell that "turn on" when they fight an infection. People with APDS usually have a low number of a certain type of B cell that has not "turned on".

The trial staff measured the number of participants' certain B cells before treatment. For the participants who had a low number, the researchers compared the change in these certain B cells from before treatment to after treatment. They found that the number of these B cells went up more in participants who took CDZ173 than in those who took the placebo. The researchers concluded this was a meaningful difference.

Change in the number of certain B cells

The graph below shows the average change in the number of certain B cells in participants' blood from before treatment to after 12 weeks of treatment. It only includes the participants who had low levels of certain B cells before treatment.



What other results were learned?

Did CDZ173 change measures of the participants' health and quality of life?

Each participant and their trial doctor answered questions to measure the effect APDS had on their health. In Part 1 and 2, the doctors' and participants' answers showed participants who took CDZ173 had fewer APDS symptoms.

The participants also answered questions about their quality of life, like their ability to go to work or school. In Part 1, the researchers couldn't conclude if CDZ173 affected quality of life due to the small number of participants. In Part 2, the researchers concluded that CDZ173 did not have a meaningful effect on quality of life.

Did CDZ173 lower signs of inflammation in the participants' blood?

The researchers looked at blood tests that measure signs of inflammation. In Part 1 and 2, the researchers concluded that some signs of inflammation went down, and some stayed about the same in participants who took CDZ173. More research is needed to know if CDZ173 has a meaningful impact on inflammation.

In Part 2, did CDZ173 shrink other swollen lymph nodes and swollen spleens?

The researchers also compared the change in size of the participants' less swollen lymph nodes and their spleens. The spleen is another organ that helps filter infections out of the blood. They found that these organs shrank more in participants who took CDZ173 than those who took the placebo.

What medical problems did the participants have?

Medical problems that happen during trials are called “adverse events”.

Trial doctors keep track of **all** adverse events that happen in trials, 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.

An adverse event is:

- Any **unwanted 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.

The adverse events in this section include any that happened during treatment and up to 1 month after completing treatment.

What medical problems did the participants have during Part 1?

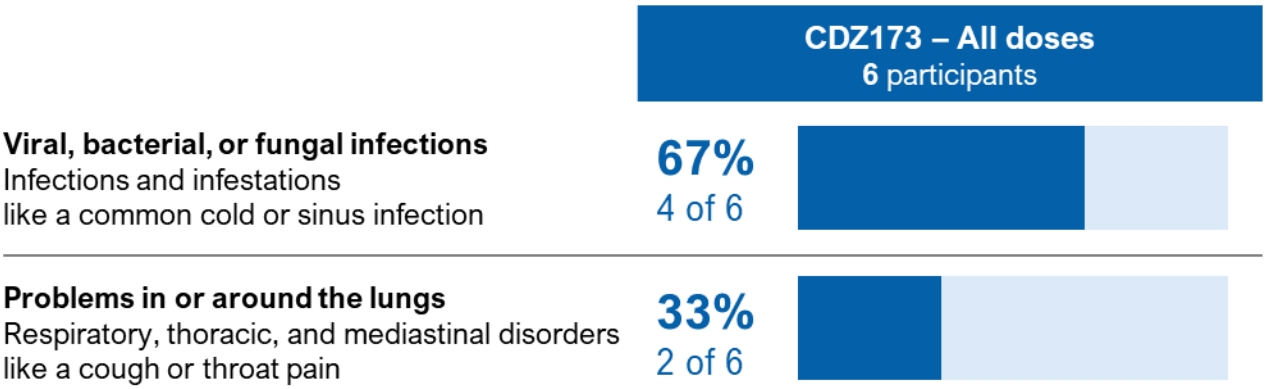
Most of the participants reported adverse events (4 out of 6 participants). None of the participants reported adverse events that were considered serious. The most common type of adverse events were viral, bacterial, or fungal infections. The researchers concluded there were no safety concerns for CDZ173 during Part 1.

What serious adverse events did the participants have?

No participants reported serious adverse events during Part 1, including death.

What other adverse events did the participants have?

4 of the 6 participants (67%) in Part 1 reported adverse events. The table below shows the types of adverse events that happened in **2 or more participants** during Part 1. Other types of adverse events were reported by fewer participants.



What medical problems did the participants have during Part 2?

Most of the participants reported adverse events (27 out of 31 participants). 5 of the 31 participants reported adverse events that were considered serious. The most common adverse event was headache. The researchers concluded there were no safety concerns for CDZ173 during Part 2.

What serious adverse events did the participants have?

5 of the 31 participants (16%) reported a total of 11 serious adverse events. The following serious adverse events happened one time.

3 of the 21 participants (14%) who took the **high dose of CDZ173** reported 5 serious adverse events:

- **Dangerously high blood levels of alcohol** | alcohol poisoning
- **State of being unconscious and unable to wake up** | coma
- **Possible sign of damage to the pancreas, kidney, or gall bladder** | lipase increased
- **Serious infection in the mastoid bone, which is behind the ear** | mastoiditis
- **Below normal body growth and weight for age** | failure to thrive

2 of the 10 participants (20%) who took the **placebo** reported 6 serious adverse events:

- **High blood pressure in the lungs and heart** | pulmonary hypertension
- **Infection of the airways in the lungs got worse** | infective exacerbation of bronchiectasis
- **Needed oxygen support** | dependence on oxygen therapy
- **Shortness of breath** | dyspnea
- **Swollen lymph nodes** | lymphadenopathy
- **UTI** | urinary tract infection

No other serious adverse events were reported, including no deaths.

What other adverse events did the participants have?

- **High dose CDZ173:** 18 of the 21 participants (86%) in Part 2 reported adverse events
- **Placebo:** 9 of the 10 participants (90%) in Part 2 reported adverse events

The table below shows the adverse events that happened in **4 or more participants**. Other adverse events were reported by fewer participants.

	High dose CDZ173 21 participants	Placebo 10 participants
Headache	24% 5 of 21	20% 2 of 10
Feeling sick to the stomach Nausea	5% 1 of 21	30% 3 of 10
Sinus infection Sinusitis	19% 4 of 21	0% 0 of 10
Infection in the nose, throat, and airways Upper respiratory tract infection	10% 2 of 21	20% 2 of 10

What was learned from this trial?

This was the first trial to learn about the safety and effects of CDZ173 in people with APDS. In this trial, the researchers learned that the high dose of CDZ173:

- Lowered the activity of PI3K delta the most
- Shrank swollen lymph nodes
- Raised the number of certain B cells in participants who had low numbers before treatment

The researchers concluded there were no safety concerns during this trial.

These are the results of a single trial. Other trials may have different results. This was one of many trials a drug goes through. This type of trial helped researchers learn about the safety of a trial drug in a small number of participants.

Where can I learn more about this and future trials?

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

- novctrd.com – search using the study number **CCDZ173X2201**
- clinicaltrials.gov – search using the number **NCT02435173**
- clinicaltrialsregister.eu/ctr-search/search – search using the number **2014-003876-22**

If more trials are planned, they will appear on the public websites above. When there, search for **CDZ173, leniolisib, APDS, or PASLI.**

Full trial title:
An open-label, non-randomized, within-patient dose-finding study followed by a randomized, subject, investigator and sponsor blinded placebo controlled study to assess the efficacy and safety of CDZ173 (Leniolisib) in patients with APDS/PASLI (Activated phosphoinositide 3-kinase delta syndrome/ p110δ-activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency)

? If you participated in the trial and have **questions** about the results, please speak with the trial doctors or staff at your trial site.

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