Clinical Trial Results Summary

NOVARTIS

A clinical trial to learn about the safety of trial drug CLR325 for people with heart failure

Thank you!

Thank you to the participants who took part in the clinical trial for the drug **CLR325**. All of the participants helped the researchers learn more about how safe CLR325 is to take.

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. An independent organization prepared this summary of the trial results.

We hope this helps the participants understand their important role in medical research.

Trial information

Trial number: CCLR325X2202
Drug studied: CLR325
Sponsor: Novartis

You can find **more information** about this trial by going to the websites listed on **page 11** of this summary.

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

This trial at a glance

What was the purpose of this trial?

Read more on **page 3**

The purpose of this trial was to learn more about the safety of the trial drug CLR325 for people with heart failure. CLR325 is designed to help the heart pump more blood.

The main question this trial was designed to answer:

- What medical problems did the participants have in this trial?
  Keeping track of the medical problems helped to learn about the safety of CLR325.

Who was in this trial?

Read more on **page 3**

- 26 men and women began this trial
- Every participant in this trial was 31 to 84 years old and had heart failure

What treatments did the participants receive?

Read more on **page 4**

The participants received one of these treatments:

- Low dose of CLR325
- Medium dose of CLR325
- High dose of CLR325
- 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.

The participants received their treatment through a needle in a vein, which is called an intravenous infusion or IV infusion.

What were the main results of this trial?

Read more on **page 6**

58% of the participants (15 of the 26 participants) had medical problems during this trial, and some of the medical problems were serious. The participants who received CLR325 had a similar number of non-serious medical problems as those who received the placebo. The most common medical problems were headache and feeling sick to the stomach.

This trial had other results along with the main results.

Read more on **page 9**

What was the purpose of this clinical trial?

Researchers are looking for better ways to treat **heart failure**, a condition in which the heart doesn't pump enough blood to the rest of the body. Heart failure can cause symptoms like shortness of breath, feeling tired, and swelling in the legs and feet. Heart failure can cause symptoms that stay the same over time or symptoms that suddenly get worse. In severe cases, it can be life threatening.

Researchers are still learning about heart failure. They suspect that a protein in the body called **apelin** may help the heart pump more blood. Sometimes, people with heart failure have lower levels of apelin in their blood.

CLR325 is a trial drug designed to help the heart pump more blood, similar to apelin. It has not yet been approved for use to treat people with heart failure. Before a drug can be approved for use, researchers do many trials to find out how safe it is and how it works.

The main question this trial was designed to answer:

- What medical problems did the participants have in this trial?
  Keeping track of the medical problems helped to learn about the safety of CLR325.

This trial was also designed to answer these questions:

- How much and how fast did CLR325 get into the participants' blood and urine?
- Did the participants develop antibodies to CLR325 or the protein apelin?

Who was in this trial?

26 participants began the trial – 23 men and 3 women. Everyone was 31 to 84 years old. Their average age was 57.

Every participant had heart failure. Most of the participants had heart failure symptoms that stayed the same over time, which is called **stable** heart failure. Some of the participants had heart failure symptoms that suddenly got worse, which is called **acute** heart failure.

People with certain medical conditions or who had recently changed their medicines couldn't be in this trial.

This trial took place in Belgium, Germany, the Netherlands, Singapore, and the United States.

For more information about who could and could not be in this trial, and the participants in this trial, visit novctrd.com. Use trial number **CCLR325X2202** to find the scientific summary.

What treatments did the participants receive?

A computer program was used to randomly assign each participant to receive one of these treatments:

- **Low dose** of CLR325: **0.25** µg/kg/minute
- **Medium dose** of CLR325: **2.5** µg/kg/minute
- **High dose** of CLR325: **8** µg/kg/minute
- **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.

µg/kg/minute is the micrograms (µg) of CLR325 a participant received for each kilogram (kg) of their body weight during each minute of treatment.

Using a computer program to assign the treatments helped make sure the results were compared as fairly as possible.

All of the participants received their treatment through a needle in a vein called an intravenous infusion or IV infusion. The IV infusion lasted 18 hours.

The participants received CLR325 slowly over 18 hours because this was the first time it was given to people. This let the trial doctors check its safety over a longer period of time.

The participants and the trial staff did not know what treatment each of the participants received during the trial. Some trials are done this way because knowing what treatment the participants receive can influence the results. Not knowing what treatment the participants receive helps make sure the results are looked at fairly.

What happened during this trial?

The trial began in May 2016 and ended in January 2019. All of the participants completed this trial.

During treatment, the trial doctors checked the participants' heart health using either of these methods:

- **Echocardiogram**: a test that uses sound waves (ultrasound) to measure how well the heart pumps blood
- **PA catheter**: a test where a long, thin tube is inserted through a blood vessel into the heart to measure how well the heart pumps blood

Here's how this trial was done:

Before treatment

- Trial doctors checked each participant's health and heart failure symptoms to make sure they could be in this trial
- 24 hours before treatment, participants couldn't change their dose of certain heart medicines

During treatment

- All the participants received their treatment through an 18-hour IV infusion
- The trial doctors checked the safety of CLR325 throughout the trial

Group 1

8 participants with **stable** heart failure

- **Medium dose CLR325** — **6** participants
- **Placebo** — **2** participants

- Trial doctors checked participants' heart health using a **PA catheter**

Safety of CLR325 was checked in Group 1 before starting Groups 2 and 3

Group 2

8 participants with **stable** heart failure

- **Low dose CLR325** — **4** participants
- **Placebo** — **4** participants

- Trial doctors checked participants' heart health using an **echocardiogram**

Group 3

10 participants with **stable** or **acute** heart failure

- **High dose CLR325** — **6** participants
- **Placebo** — **4** participants

- Trial doctors checked participants' heart health using a **PA catheter**

After treatment

- About 10 days and 28 days after their last dose, participants visited the trial site for the trial doctors to check their health

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.

What medical problems did participants have during the trial?

Medical problems that happen during clinical trials are called **adverse events**. Trial doctors looked for any adverse events when they checked the participants' health during the trial. The participants also reported adverse events.

Many trials are needed to know if a drug or treatment causes an adverse event. Trial doctors keep track of all adverse events that happen in trials, even if they do not think the adverse events might be related to the trial treatments.

What is an adverse event?

- An **adverse event** is any unwanted sign or symptom that participants have during a trial
- It is 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

58% of the participants (15 of the 26 participants) had adverse events during this trial, and some adverse events were serious. The participants who received CLR325 had a similar number of non-serious adverse events as those who received the placebo.

The trial doctors looked for any adverse events when they checked the participants' blood and urine samples and during the visits to the trial site. The participants also reported adverse events.

The clinical trial team concluded that all the doses of CLR325 were safe for the participants in this trial. Also, the number of adverse events went up as the dose of CLR325 went up, as shown in the table on the next page.

The participants who had adverse events

Participants who had:	Low dose CLR325 out of 4 participants	Medium dose CLR325 out of 6 participants	High dose CLR325 out of 6 participants	Placebo out of 10 participants
Serious adverse events	0% 0 of 4	33% 2 of 6	33% 2 of 6	0% 0 of 10
Non-serious adverse events	25% 1 of 4	50% 3 of 6	67% 4 of 6	70% 7 of 10
Left this trial due to adverse events	0% 0 of 4	0% 0 of 6	0% 0 of 6	0% 0 of 10

What serious adverse events did the participants have?

2 of the 6 participants who received the **medium dose** of CLR325 had a total of 2 serious adverse events:

- **Infection of lung airways** (bronchitis)
- **Sign of liver injury** (hepatic enzyme increased)

2 of the 6 participants who received the **high dose** of CLR325 had a total of 4 serious adverse events:

- **Heart failure that got worse** (cardiac failure congestive)
- **Heart attack** (acute myocardial infarction)
- **Mental and emotional confusion** (delirium)
- **Infection of lung airways** (bronchitis)

During this trial, no other serious adverse events were reported, including deaths.

What non-serious adverse events did the participants have?

Some of the participants reported adverse events that were not serious. The most common adverse events were headache and feeling sick to the stomach.

The table below shows the non-serious adverse events that happened **to at least 2 of the participants** during this trial. There were other adverse events reported by fewer participants.

Non-serious adverse events

	Low dose CLR325 out of 4 participants	Medium dose CLR325 out of 6 participants	High dose CLR325 out of 6 participants	Placebo out of 10 participants
Headache	25% 1 of 4	0% 0 of 6	0% 0 of 6	30% 3 of 10
Feeling sick to the stomach Nausea	25% 1 of 4	0% 0 of 6	17% 1 of 6	10% 1 of 10
Dizziness	0% 0 of 4	0% 0 of 6	33% 2 of 6	0% 0 of 10
Itching at the injection site Infusion site pruritus	25% 1 of 4	0% 0 of 6	0% 0 of 6	10% 1 of 10
Low blood pressure Hypotension	0% 0 of 4	0% 0 of 6	33% 2 of 6	0% 0 of 10

For more information about the adverse events reported by the participants in this trial, visit novctrd.com. Use trial number **CCLR325X2202** to find the scientific summary.

What other results were learned?

The clinical trial team also learned more about:

How much and how fast did CLR325 get into the participants' blood and urine?

Trial staff measured the levels of CLR325 in the participants' blood and urine. They also measured the levels of CLR325's metabolite. A metabolite is a substance that forms when CLR325 is broken down by the body.

The levels of CLR325 and its metabolite in the blood were what the clinical trial team expected based on a past trial in healthy participants. The team found that the body removed some of the trial drug and metabolite through urine.

Did the participants develop antibodies to CLR325 or the protein apelin?

The trial staff checked the participants' blood for antibodies that attach to CLR325. Sometimes, antibodies attach to a drug when the drug gets in the blood. This can make the trial drug not work as well or affect how long it stays in the blood.

Because CLR325 is similar to the protein apelin, trial staff also checked the participants' blood for antibodies to apelin.

The clinical trial team checked the participants' blood for these antibodies before and after treatment. This helped find out if the participants had these antibodies before the trial or if they developed antibodies during the trial.

What are antibodies?

Antibodies are a part of the immune system. The immune system is made of cells and proteins that protect the body from foreign substances, such as bacteria and viruses.

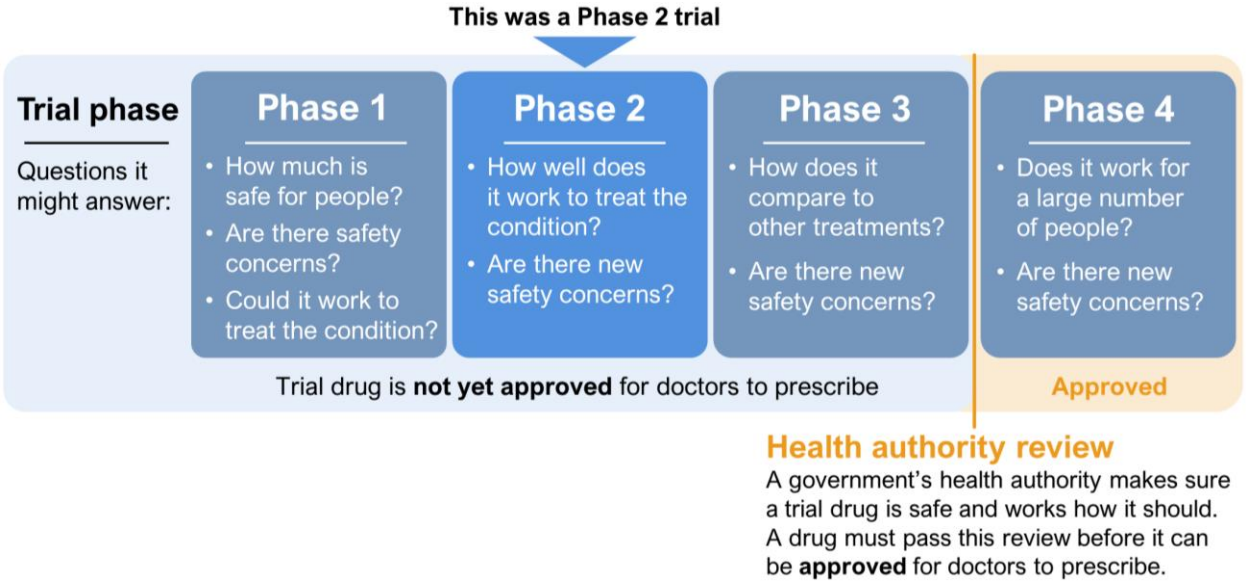
Antibodies are a type of immune system protein that find and attach to foreign substances.

The team found that the participants did not develop antibodies to CLR325 or apelin.

What was learned from this trial?

This was the first trial to learn how safe CLR325 is for people with heart failure. The clinical trial team found that the participants who received CLR325 had a similar number of medical problems as those who received the placebo. The team concluded that CLR325 was safe for the participants in this trial.

This was a Phase 2 clinical trial, which tests the safety of a trial drug in a small number of participants. This was one of many trials a drug must go through before it can be approved for doctors to prescribe. The chart below shows these phases and what questions they're designed to answer.



The results presented here are for one trial. One trial cannot give a complete picture of the benefits and risks of a trial drug. The results of many trials are needed to find out which treatments can be used for people who have heart failure. This summary shows only the main results from this trial. Other trials may provide new information or different results.

Where can I learn more about this and future clinical trials?

This is a summary of the results for one clinical trial.

You can find detailed results and more information about this trial on the Novartis Clinical Trial Results website:

1. Visit novctrd.com
2. Click on “Clinical trial results and trial summary for patients” at the top right of the page
3. Read and scroll down, then click “I accept” to agree to use the information and the website
4. Select “Search by study number” on the bottom left of the page
5. Type **“CCLR325X2202”** in the search box and click search

If you would like to view the website in a language other than English, you can click the “Google Translate” button on the top right of the page.

If you were in this clinical trial and have questions about the results, please speak with the doctor or staff where you took part in this clinical trial.

This clinical trial was registered on the following websites:

- ClinicalTrials.gov – https://clinicaltrials.gov/
  To find this trial, type **CCLR325X2202** in the **Other terms** search box
- European Union Clinical Trials Register – https://www.clinicaltrialsregister.eu/ctr-search
  To find this trial, type **CCLR325X2202** in the search box

Full trial title:

A randomized, subject and investigator-blind, placebo-controlled study of CLR325 in chronic stable heart failure patients

If more clinical trials are planned, they will appear on the public websites listed on the previous page. When there, search for **CLR325**.

Thank you!

Novartis would like to thank all of the people who participated in this clinical trial. The participants made this clinical trial possible and helped researchers answer important health questions and learn about a possible medical treatment. Many volunteers and many clinical trials are needed to advance medical science.

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