NOVARTIS

Clinical Trial Results Summary

A clinical trial to learn about the safety of LCZ696 in Japanese participants with heart failure who completed the CLCZ696D2301 (PARAGON-HF) trial

Protocol number: CLCZ696D1301E1

Thank You!

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. Thank you for taking part in this trial for the drug LCZ696, which has two substances, sacubitril and valsartan. You helped researchers learn more about the safety of LCZ696 in Japanese people with heart failure who completed the earlier CLCZ696D2301 trial.

As a clinical trial participant, you belong to a large community of people around the world. Your invaluable contribution to medicine and healthcare is greatly appreciated.

This summary only shows the results of a single clinical trial. Other clinical trials may have different findings. Researchers and health authorities, such as the Pharmaceuticals and Medical Devices Agency (PMDA), look at the results of many clinical trials to understand which drugs work and if they are safe. It takes many people in multiple clinical trials around the world to advance medical science and healthcare. If you have any questions about these trial results, please talk to the doctor or staff at your trial site.

How long was this trial?

This trial started in May 2019 and ended in November 2019. The sponsor ended this trial early because the results of the earlier CLCZ696D2301 trial showed that LCZ696 was not better than valsartan in treating participants with heart failure based on the trial criteria for early termination.

When the trial ended, the researchers collected information on the trial treatment (LCZ696) and created a report of the trial results. This summary is based on that report.

Why was the research needed?

Heart failure with preserved ejection fraction (HFpEF) is a long-term condition in which the heart muscles lose their ability to relax normally. This means that the heart cannot fill with the normal amount of blood in between each beat, and pumps out less blood than the body needs. It causes the common symptoms of heart failure such as shortness of breath, weakness, feeling tired, and swollen ankles and legs, to be noticeable even at rest.

Currently, there is no approved treatment for HFpEF. LCZ696 is being tested for the treatment of HFpEF. It is approved in many countries for the treatment of heart failure with reduced ejection fraction (HFrEF). HFrEF is a long-term condition where the heart is weak and cannot pump enough blood through the body with each heartbeat. This reduces the supply of oxygen the body needs to function normally. In Japan, LCZ696 is approved for the treatment of heart failure (HF).

In this trial, researchers wanted to know more about the safety of LCZ696 in Japanese participants with HFpEF who completed the earlier CLCZ696D2301 trial.

Trial drug

The drug given in this trial was:

LCZ696: the trial drug, which has two substances, sacubitril and valsartan.

Throughout the trial, the participants continued to take other medicines for long-term heart failure as prescribed by their doctor except for certain blood pressure lowering drugs called angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), and renin inhibitors. If participants had to take ACEIs, ARBs, or renin inhibitors then the trial drug had to be discontinued temporarily.

Trial purpose

The main question the researchers wanted to answer in this trial was:

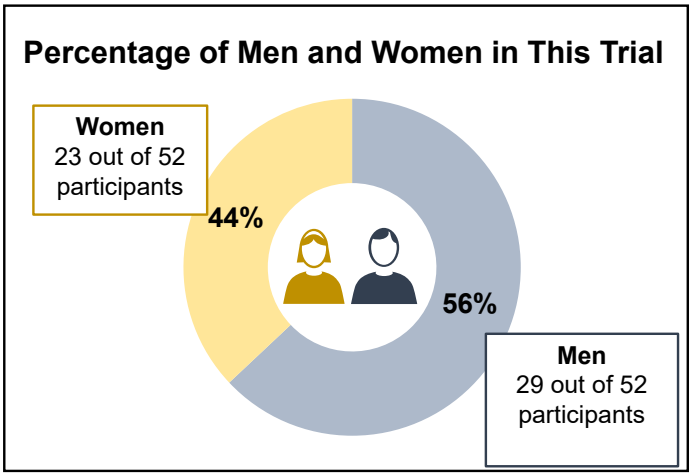
How many participants had medical problems during this trial?

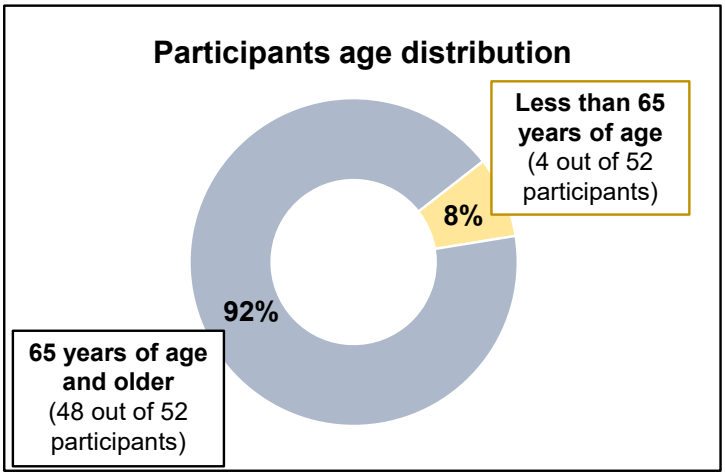
Medical problems that happen in clinical trials are called “adverse events”. Adverse events are defined on Page 5.

Who was in this trial?

A total of 52 participants from Japan who had completed the earlier CLCZ696D2301 trial participated in this trial.

The average age of participants was 77 years. Participants’ age ranged from 55 to 93 years. About 56% of the trial participants, or 29 out of 52, were men.





What kind of trial was this?

This was an open-label trial, which means that both the researchers and the participants knew that LCZ696 was given to participants.

What happened during this trial?

During screening

The participants who completed the earlier CLCZ696D2301 trial were allowed to participate in this extension trial as long as it was safe to do so. Eligible participants were enrolled in this trial over a period of up to about 6 months after the earlier CLCZ696D2301 trial results were known.

During treatment

Participants started on the same dose of LCZ696 or equivalent to the dose they were taking when they completed the earlier CLCZ696D2301 trial. Dose adjustments were permitted based on the participants' tolerability and the judgment of the trial doctor. The highest dose of LCZ696 that could have been given during this trial was 200 milligrams (mg) twice daily.

The participants could have received LCZ696 until it became available in the market, or for a period of up to 24 months from the first participant enrolled in the trial, whichever came first.

However, this study was terminated early because the results of the earlier CLCZ696D2301 trial showed that LCZ696 was not better than valsartan in treating participants with heart failure.

Throughout the trial, researchers monitored the health of the participants.

What medical problems did the participants have during the trial?

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. During a trial, all adverse events are recorded, whether or not they are thought to be caused by the trial drug. When new drugs are being studied, researchers keep track of all adverse events participants have.

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

An adverse event is an unwanted sign, symptom, or disease 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 drug.

How many participants had adverse events?

The adverse events presented in this summary are those that happened from the start of the treatment up to completion (27 weeks) of the trial. None of the participants died during the trial.

Number of Participants (%) With Adverse Events

	LCZ696 (Out of 52 participants)
At least 1 adverse event	40 (77%)
At least 1 serious adverse event	8 (15%)
Stopped drug due to adverse event	2 (4%)

What were the most common non-serious adverse events?

The most common non-serious adverse events that happened in at least 5% (5 out of 100) of participants are presented below.

Number of Participants (%) With Most Common Non-Serious Adverse Events

	LCZ696 (Out of 52 participants)
Diarrhea Diarrhoea	5 (10%)
Low blood pressure Hypotension	3 (6%)
Low potassium level in the blood Hypokalaemia	4 (8%)
Nose and throat infection Nasopharyngitis	7 (13%)

What were the serious adverse events?

Each serious adverse event occurred once. The serious adverse events included:

- Brain stroke due to a blood clot from elsewhere in the body (Embolic stroke)
- Scar-like tissue over the central area in the back of the eye (Macular fibrosis)
- Feeling sick to the stomach (Nausea)
- Fracture in backbone (Spinal compression fracture)
- Headache
- Worsening of heart failure (Cardiac failure chronic)
- Irregular heartbeat (Atrial fibrillation)
- Part of the intestine comes through the abdominal muscles (Inguinal hernia)
- Stomach flu (Gastroenteritis)

How many participants stopped trial drug due to adverse events?

During the trial, 2 out of 52 (4%) of participants stopped LCZ696 early due to adverse events of worsening of heart failure (Cardiac failure chronic) and low blood pressure (Hypotension).

How was this trial useful?

This trial helped researchers learn about the safety of LCZ696 in Japanese participants with HFpEF who completed the earlier CLCZ696D2301 trial. Safety results from this trial were similar to the safety results in the earlier CLCZ696D2301 trial. Results from this trial may be used in other clinical trials for people with HFpEF.

If you have any questions about these trial results, please talk to the doctor or staff at your trial site.

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). Use the study identifier CLCZ696D1301E1 in the search field.

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

- www.clinicaltrials.gov Use the NCT identifier NCT03909295 in the search field.

Full clinical trial title: A multicenter, open-label study to evaluate the safety and tolerability of LCZ696 treatment in Japanese heart failure patients (NYHA Class II-IV) with preserved ejection fraction after CLCZ696D2301 (PARAGON-HF)

Thank you

Thank you for taking part in this trial. As a clinical trial participant, you belong to a large community of people around the world. You helped researchers answer important health questions and test new medical treatments.

NOVARTIS

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

1-888-669-6682 (US); +41-61-324-1111 (EU);
www.novartisclinicaltrials.com