Clinical Trial Results Summary

A clinical trial to learn about the effects of LCZ696 compared with enalapril to improve the ability to exercise by participants with a heart that has a reduced ability to pump blood

Protocol number: CLCZ696BDE01

Thank You!

Novartis, the sponsor of this clinical trial, would like to 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 effects of LCZ696 compared with enalapril to improve the ability to exercise by participants with a heart that has a reduced ability to pump blood.

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 Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA) in Europe, 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 was designed so that an individual participant could take part for about 3 months. The trial started in July 2016 and ended in November 2019. The entire duration, from enrolling the first participant to the last participant completing the trial was about 3 years and 5 months.

The researchers completed this trial as planned. When the trial ended, the researchers collected information on the trial treatments (LCZ696 and enalapril) and created a report of the trial results. This summary is based on that report.

Why was the research needed?

Heart failure with reduced ejection fraction (HFrEF) is a chronic 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. It causes the common symptoms of heart failure, such as shortness of breath, weakness, feeling tired, and swollen ankles and legs.

People with HFrEF have difficulty in performing daily physical activities and exercise due to the reduced availability of oxygen in the body. This affects their quality of life.

In this trial, researchers were looking for a way to improve the exercise ability in participants with HFrEF.

Trial drugs

The drugs given in this trial were:

- **LCZ696**: the trial drug, which has two substances, sacubitril and valsartan. It is approved for the treatment of HFrEF.
- **Enalapril**: a comparator drug, which is approved as a standard treatment for HFrEF.

As the drugs given in the trial looked different, participants were also given a sugar pill along with the trial drugs. This was done to ensure that the researchers and participants did not know who received which drug.

Before starting trial treatment, the participants had to stop taking certain blood pressure lowering drugs called angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-receptor blockers (ARBs).

Throughout the trial, the participants were allowed to continue taking their other usual medicines for chronic heart failure as prescribed by their doctor.

Trial purpose

In this trial, researchers compared the effects of LCZ696 with enalapril to find out if these drugs improved the ability of participants' with HFrEF to exercise.

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

> At the end of 3 months of treatment compared with the start of the trial, did participants who received LCZ696 uptake and utilize more oxygen while exercising than those who received enalapril?

The other questions researchers wanted to answer in this trial were:

- At the end of 3 months of treatment compared with the start of the trial, did participants who received LCZ696 improve their capacity to exercise (measured in Watts) more than participants who received enalapril?
- Were the participants' perception of effort they spent when doing the exercise test at the beginning of the trial and after 3 months similar for both treatment groups?

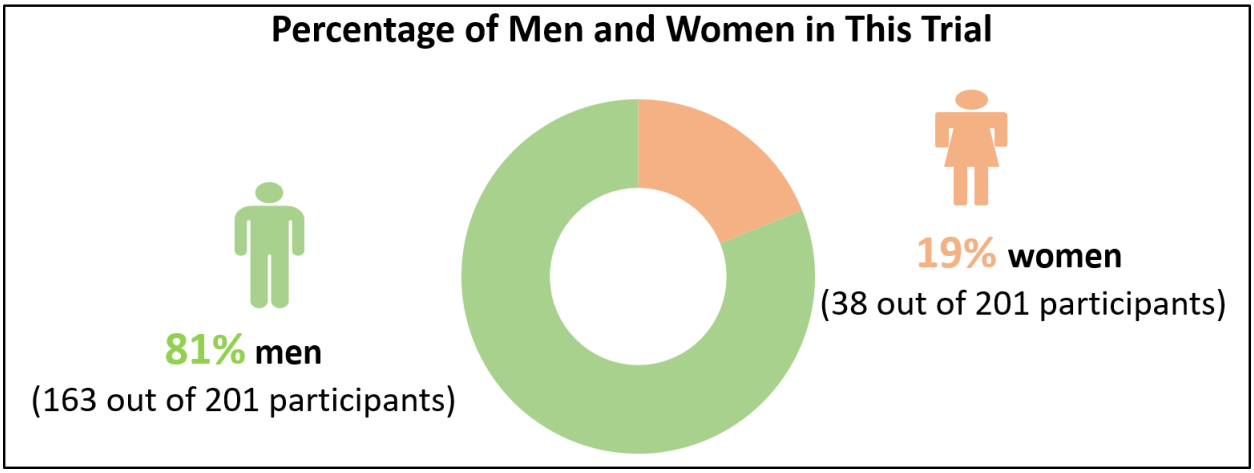
Who was in this trial?

The participants could take part in this trial if they:

- were at least 18 years of age.
- were diagnosed with Class III New York Heart Association HFrEF, meaning they were unable to do normal physical activities and only felt comfortable when resting.
- had reduced ability to uptake and utilize oxygen.
- were on ACEI or ARBs for at least 4 weeks before entering the trial.
- were receiving standard treatment for HFrEF and were on a stable dose, as prescribed by their doctor, for at least 4 weeks before entering the trial.

A total of 201 participants at 34 centers in Germany participated in this trial.

The average age of participants was 67 years. Participants' age ranged from 31 to 88 years. The majority of participants, 163 out of 201 (81%) were men.



What kind of trial was this?

This was a double-blind trial. This means that none of the participants, trial doctors, or trial staff knew what treatment participants were receiving. Some trials are done this way because knowing what treatment each patient is getting can affect the results of the trial. Doing a trial this way helps to make sure that the results are looked at with fairness towards all treatments.

What happened during this trial?

Participants went through a screening period of 2 weeks to confirm that they could take part in the trial.

After screening, the researchers randomly assigned the participants into two treatment groups to receive:

- **LCZ696 Group** – LCZ696 200 mg (97 mg of sacubitril and 103 mg of valsartan) twice daily.
- **Enalapril Group** – Enalapril 10 mg twice daily.

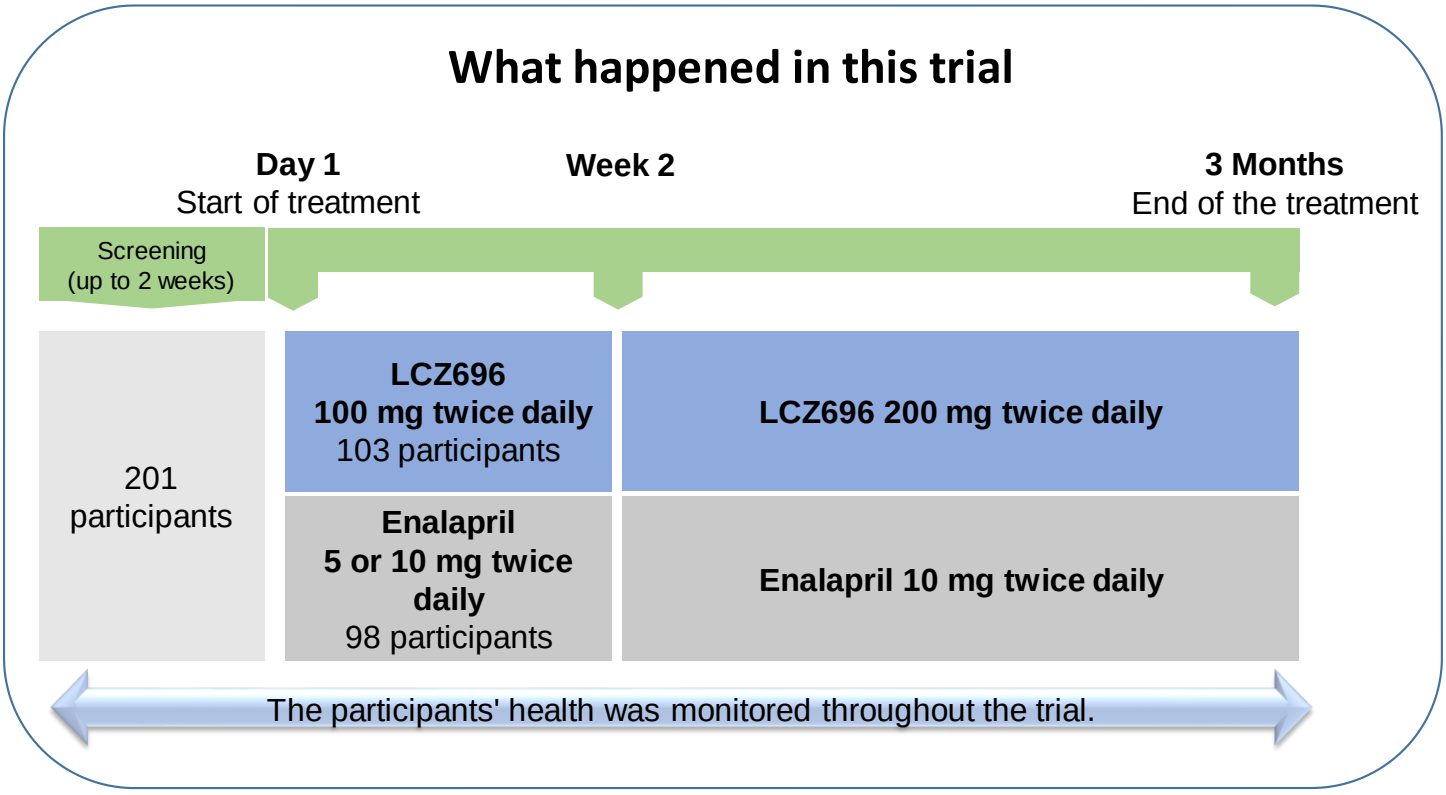
This process is called randomization. This means that each participant had an equal chance of being assigned to any group.

For the first 2 weeks of treatment, the participants were given a dose, twice a day, of 100 mg LCZ696 or 5 mg enalapril. The trial drug dose was doubled after the first 2 weeks as long as:

- the participants' blood pressure, kidney function and potassium levels in the blood were considered normal.
- the participants did not have signs and symptoms of any condition that would require them to stop the trial treatment.

Participants in the enalapril group who were already on a dose of more than 10 mg enalapril twice a day or equivalent for other blood pressure lowering drugs before entering the trial started at the 10 mg enalapril dose.

The participants performed an exercise test called spiroergometry on a cycle ergometer at screening, and at 6 weeks and 3 months after starting treatment. The participants' health was monitored throughout the trial. All participants received treatment for 3 months (12 weeks) unless the treatment was interrupted or discontinued.



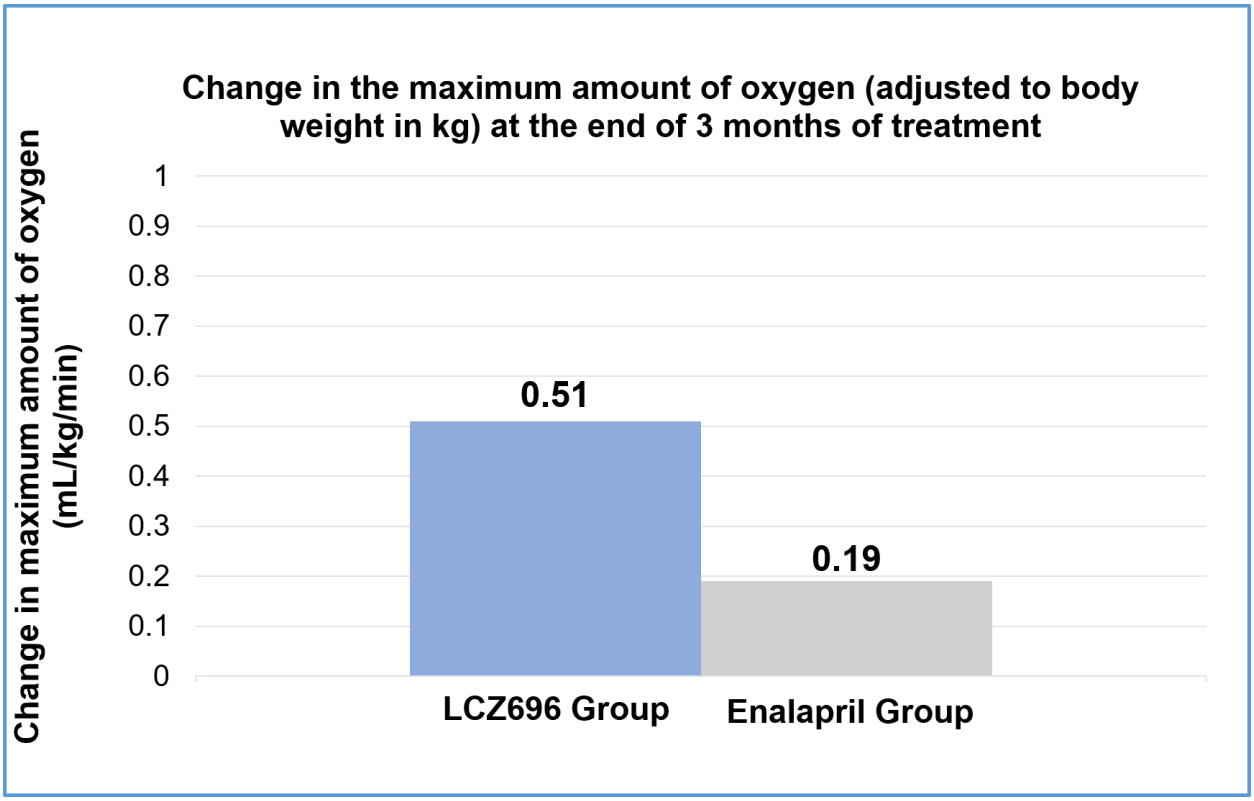
What were the key results of this trial?

This is a summary of the average results for all participants in different treatment groups. It does not show the results of each individual participant. Results of individual participants could be different from the results of the total group of participants. A detailed presentation of the results can be found on the websites listed at the end of this summary.

At the end of 3 months of treatment compared with the start of the trial, did participants who received LCZ696 uptake and utilize more oxygen while exercising than participants who received enalapril?

The participants' ability to exercise was assessed by measuring the maximum amount of oxygen they could uptake and utilize while doing the exercise test. The amount of oxygen that the participants could uptake and utilize was measured in mL per minute and adjusted for their body weight (kg).

Researchers could not find a meaningful difference between the groups in the change in the maximum amount of oxygen that participants could uptake and utilize while exercising.



What were the other results of this trial?

At the end of 3 months of treatment compared with the start of the trial, did participants who received LCZ696 improve their capacity to exercise (measured in watts) more than participants who received enalapril?

During the exercise test, the participants' capacity to exercise was measured in watts, a unit of energy. The watts measured how much power the participants were producing while doing the exercise test.

Researchers could not find a meaningful difference between the groups in the capacity to exercise (production of watts) at the end of 3 months of treatment.

Were the participants' perception of effort they spent when doing the exercise test at the beginning of the trial and after 3 months similar for both treatment groups?

Participants in both groups had the same perception of effort they spent when doing the exercise test at the beginning of the trial and after 3 months of treatment.

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?

140 out of 201 participants (70%) had 1 or more adverse events. During the trial, 9 out of 201 participants (5%) stopped the trial because of adverse events. Serious adverse events happened in 26 out of 201 participants (26%) in the trial. 3 participants died during this trial.

Number of Participants (%) With Adverse Events

	LCZ696 Group (Out of 103 Participants)	Enalapril Group (Out of 98 Participants)
At least 1 adverse event	77 (75%)	63 (64%)
At least 1 serious adverse event	12 (12%)	14 (14%)
Stopped trial due to adverse event	4 (4%)	5 (5%)
Death	2 (2%)	1 (1%)

What were the most common non-serious adverse events?

The most common non-serious adverse events that happened in at least 5% of participants in any group are presented in the next table.

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

	LCZ696 Group (Out of 103 Participants)	Enalapril Group (Out of 98 Participants)
Cough	3 (3%)	9 (9%)
Difficulty in breathing	2 (2%)	6 (6%)
Feeling dizzy	14 (14%)	6 (6%)
Feeling tired	2 (2%)	7 (7%)
High potassium levels in the blood	9 (9%)	3 (3%)
Low blood pressure	27 (26%)	11 (11%)
Nose and throat infection	9 (9%)	3 (3%)

What were the most common serious adverse events?

The next table shows the most common serious adverse events that happened in at least 2% of participants in any group. A full list of the serious adverse events is available on the websites listed at the end of this document.

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

	LCZ696 Group (Out of 103 Participants)	Enalapril Group (Out of 98 Participants)
Fainting	0 (0%)	2 (2%)
Fast heartbeat	2 (2%)	0 (0%)
Irregular heartbeat	2 (2%)	1 (1%)
Lung infection	2 (2%)	0 (0%)
Worsening of heart failure	1 (1%)	2 (2%)

How many participants stopped trial drug due to adverse events?

During the trial, 6% (6 out of 103) of participants stopped LCZ696 early due to adverse events such as difficulty in breathing, heart attack, high blood urea, decreased glomerular filtration rate, high potassium level in the blood, infection throughout the body, and swelling of the eyelid.

High blood urea, decreased glomerular filtration rate, and high potassium level in the blood may indicate kidney damage or abnormal kidney function.

During the trial, 9% (9 out of 103) of participants stopped enalapril early because of adverse events such as difficulty in breathing, upper stomach pain, heart attack, circulatory collapse, constipation, cough, feeling dizzy, incurable brain cancer, difficulty sleeping, swelling of the pancreas, fits, and ringing noise in ears.

How was this trial useful?

This trial helped researchers learn about the effects of LCZ696 compared with enalapril to improve the ability to exercise by participants with HFrEF. No difference was seen between the treatment groups on oxygen intake or capacity to exercise. Participants in both groups had the same perception of effort when doing the exercise test.

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 CLCZ696BDE01 in the search field.

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

- www.clinicaltrials.gov Use the NCT identifier NCT02768298 in the search field.
- https://www.clinicaltrialsregister.eu/ctr-search/search Use the EudraCT identifier 2015-004632-35 in the search field.

Full clinical trial title: A randomized, double-blind, active-controlled study to assess the effect of LCZ696 compared with enalapril to improve exercise capacity in patients with heart failure with reduced ejection fraction (HFrEF)

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.

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1-888-669-6682 (US); +41-61-324-1111 (EU);
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