NOVARTIS

Clinical Trial Results Summary

A clinical trial to learn about the effects and safety of LCZ696 compared to individual therapy in participants with heart failure

Protocol number: CLCZ696D2302

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 effects and safety of LCZ696 in people with heart failure.

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 6 months. The trial started in August 2017 and ended in October 2019. The entire duration, from enrolling the first participant to the last participant completing the trial, was 2 years and 2 months.

The researchers completed this trial as planned. When the trial ended, the researchers collected information on the trial treatments: LCZ696 and individual therapy (enalapril, valsartan, or placebo) 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 (**HF with preserved EF**) is a long-term condition in which the heart muscles lose their ability to relax normally. This means that the heart becomes stiffer and is unable to 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.

Currently, there is no approved treatment for **HF with preserved EF**. LCZ696 is being tested for the treatment of **HF with preserved EF**. It is approved in many countries for the treatment of heart failure with reduced ejection fraction (**HF with reduced EF**). HF with reduced EF 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.

In this trial, researchers wanted to find out if LCZ696 compared to individual therapy (enalapril, valsartan or placebo) could give better relief for heart failure signs and symptoms and if it helps patients exercise better. Enalapril and valsartan are drugs approved for treating high blood pressure and heart failure.

Trial drugs

The drugs given in this trial were:

LCZ696	The trial drug has two substances, sacubitril and valsartan. Participants received LCZ696 as oral tablets.
Enalapril	An individual therapy. Participants received enalapril as oral tablets.

Valsartan	An individual therapy. Participants received valsartan as oral tablets.
Placebo	The placebo individual therapy looked like the trial drug, but did not have any medicine in it. Using a placebo helps researchers better understand the effect of a trial drug by making sure that the changes were not happening by chance. Participants received placebo as oral tablets.

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

Trial purposes

The main questions the researchers wanted to answer in this trial were:

1. Did participants who received LCZ696 have a greater reduction in the blood levels of *NT-proBNP compared with individual therapy after 3 months of treatment?

*N-terminal pro-brain natriuretic peptide (NT –proBNP) are proteins produced in large amounts by the heart when it is not working properly as in heart failure. It correlates strongly with stress put on the walls of the heart.

2. Did participants who received LCZ696 walk farther compared with individual therapy on the 6-minute walk test (6-MWT) after 6 months of treatment?

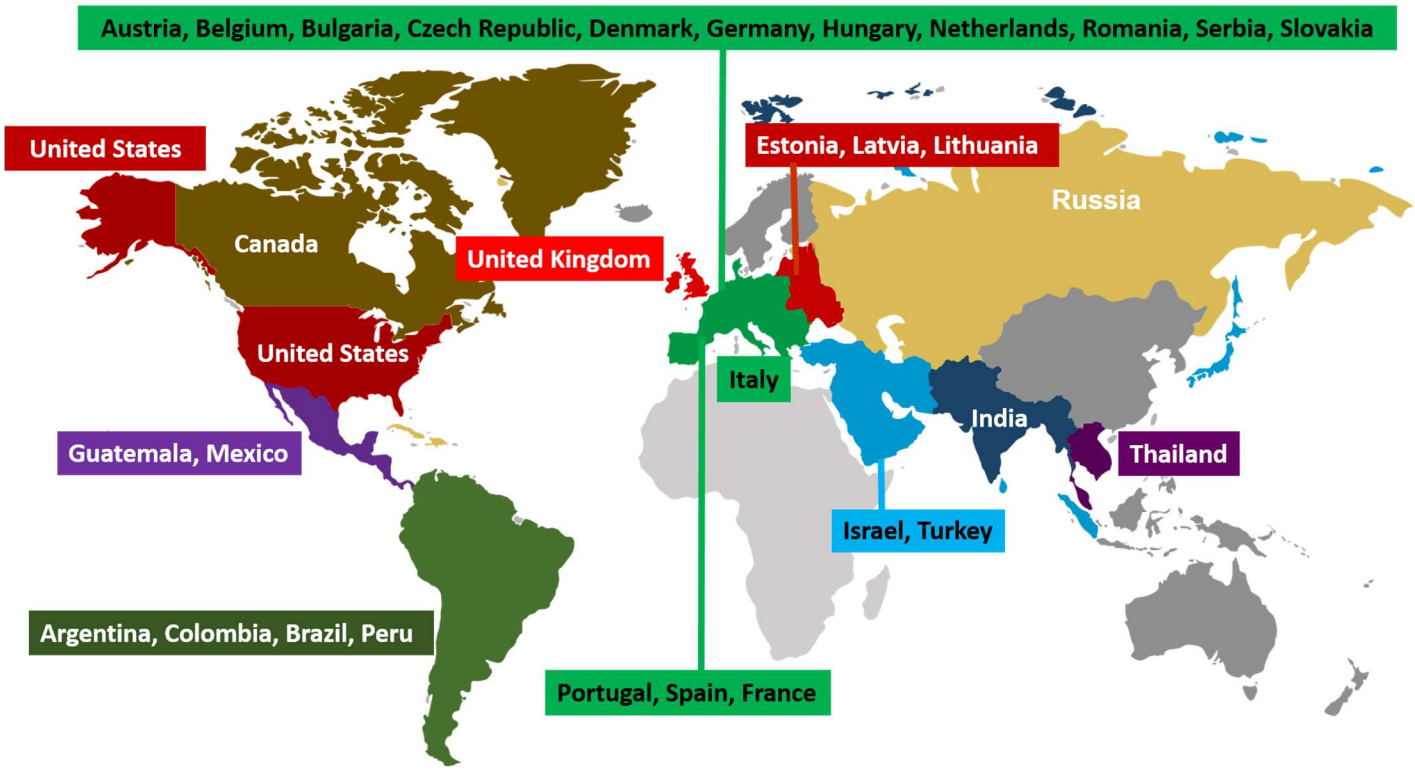
Who was in this trial?

The participants could take part in this trial if they:

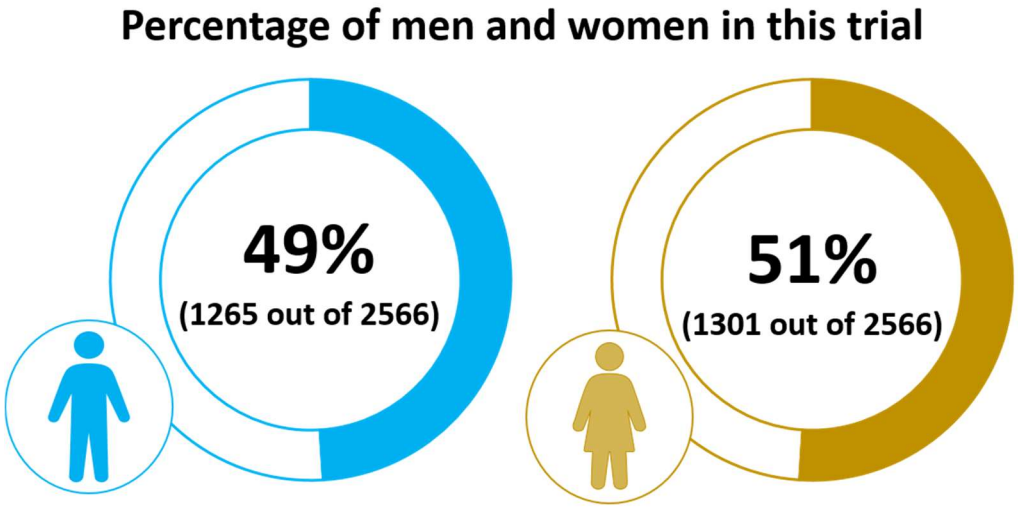
- were 45 years of age and above,
- had **HF with preserved EF** with left ventricular ejection fraction (LVEF) greater than 40% at screening. LVEF is the measurement of the percentage of blood that is being pumped out of the left ventricle of the heart (the main pumping chamber) with each contraction,
- reported mild to severe limitations to their quality of life due to heart failure,
- had a high level of **NT-proBNP*** (at least 220 picograms per milliliter [pg/mL]),
- were on a diuretic (drugs that increase the amount of urine and lower blood pressure) to treat symptoms of heart failure.

For **NT-proBNP definition, please refer to Page 3 section Trial Purposes, question 1.*

A total of 2572 participants from 32 countries were enrolled in this trial.



The average age of participants was 73 years. Participants' age ranged from 44 to 92 years, even though the minimum age for entering the trial was 45 years. The majority of participants were women, 1301 out of 2566 (51%).



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 toward all treatments.

What happened during this trial?

During screening

To find out if participants qualified to take part in this trial, researchers conducted certain tests like:

- a full body checkup,
- an electrocardiogram (often called ECG) to measure the heart's electrical activity,
- blood and urine tests,
- an ultrasound of the heart, and
- a 6-minute walk test (6-MWT) to measure the distance that participants could walk in 6 minutes.

Researchers also reviewed participant's medical history.

Randomization

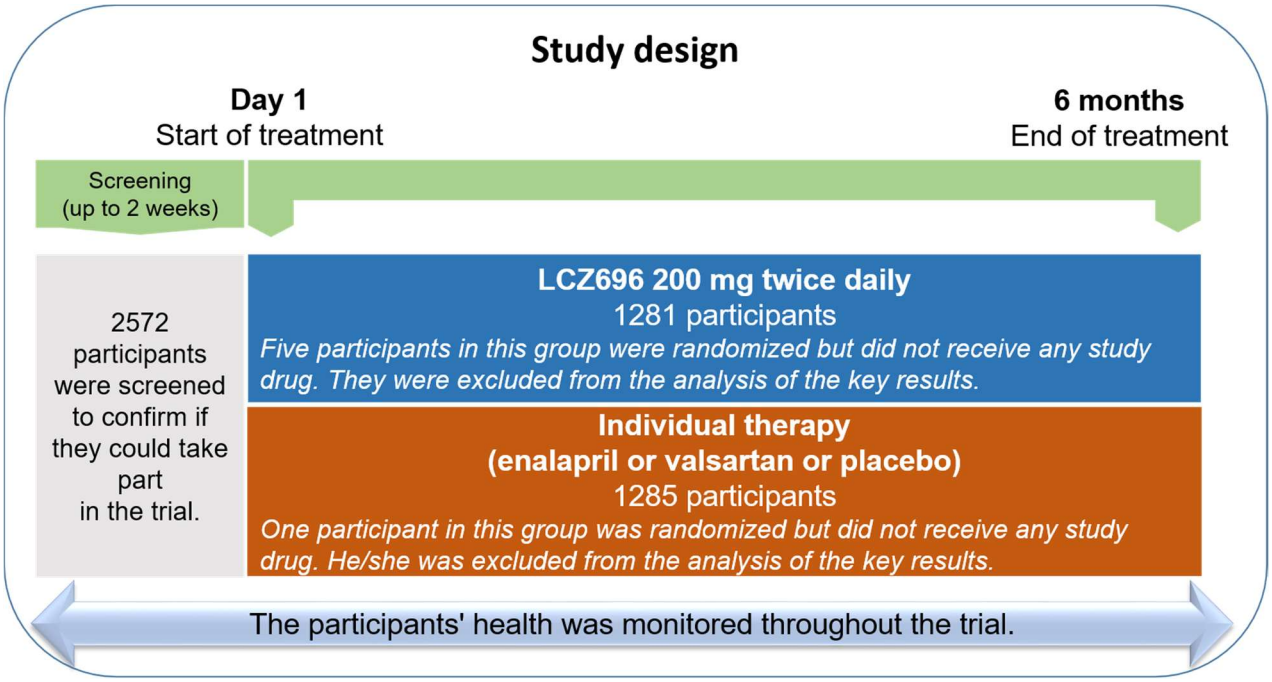
Eligible participants were first divided into one of the 3 groups depending on whether they were taking **ACEIs**, **ARBs**, or no ACEIs/ARBs before entering the study. Participants in each group were randomly assigned to receive either LCZ696 or the individual therapy (enalapril, valsartan or placebo). This process is called randomization. This means that each participant had an equal chance of being assigned to any group.

- **ACEI group**: Participants who were previously treated with ACEIs received either LCZ696 or enalapril,
- **ARB group**: Participants who were previously treated with ARBs received either LCZ696 or valsartan,
- **No ACEI/ARB group**: Participants who were not previously treated with ACEIs/ARBs received either LCZ696 or placebo.

During treatment

Participants were switched to a starting dose of the study drug which was in line with the dose of their prior individual therapy. Participants who were not previously treated with ACEIs/ARBs started on the lowest LCZ696 dose permitted or matching placebo. The target doses were:

- LCZ696 200 milligram (mg) oral tablets twice a day
- Enalapril 10 mg oral tablets twice a day
- Valsartan 160 mg oral tablets twice a day



Dose adjustments were permitted based on the participants' tolerability and the judgment of the trial doctors.

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

What were the key results of this trial?

This is a summary of the average results for participants treated with LCZ696 and in participants treated with the individual therapy (enalapril, valsartan or placebo). It does not show the results of each participant. Results of a single participant 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.

The results for the key questions were analyzed for 2566 participants.

Did participants who received LCZ696 have a greater reduction in the blood levels of NT-proBNP* compared with individual therapy after 3 months of treatment?

To answer this question, researchers collected blood samples from participants at the start of the trial and after 3 months of treatment to measure the blood levels of **NT-proBNP.**

After 3 months of treatment, participants in **LCZ696 group** showed approximately **16%** greater reduction of blood **NT-proBNP*** levels compared to participants in the **individual therapy group**, suggesting less stress on the walls of the heart.

** For **NT-proBNP** definition, please refer to Page 3 section Trial Purposes, question 1.*

Did participants who received LCZ696 walk farther compared with individual therapy on the 6-minute walk test (6-MWT) after 6 months of treatment?

To answer this question, researchers asked the participants to walk for 6 minutes, at the start of the trial and then again, after 6 months of treatment. The distance walked was measured in meters.

After 6 months of treatment, participants in both groups showed a slight improvement in the capacity to walk.

At the start of the trial, participants in **LCZ696 group** could walk an average distance of 292 meters and participants in the **individual therapy group** could walk an average distance of 297 meters.

After 6 months of treatment, participants in **LCZ696 group** had a slightly smaller increase (change was 10 meters) compared to participants in the **individual therapy group** (12 meters), but the difference between the groups was likely to be by chance rather than a difference caused by the 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, or could be due to pre-existing medical conditions.

How many participants had adverse events?

The safety results were analyzed for all the participants who took the trial drug (2564 participants).

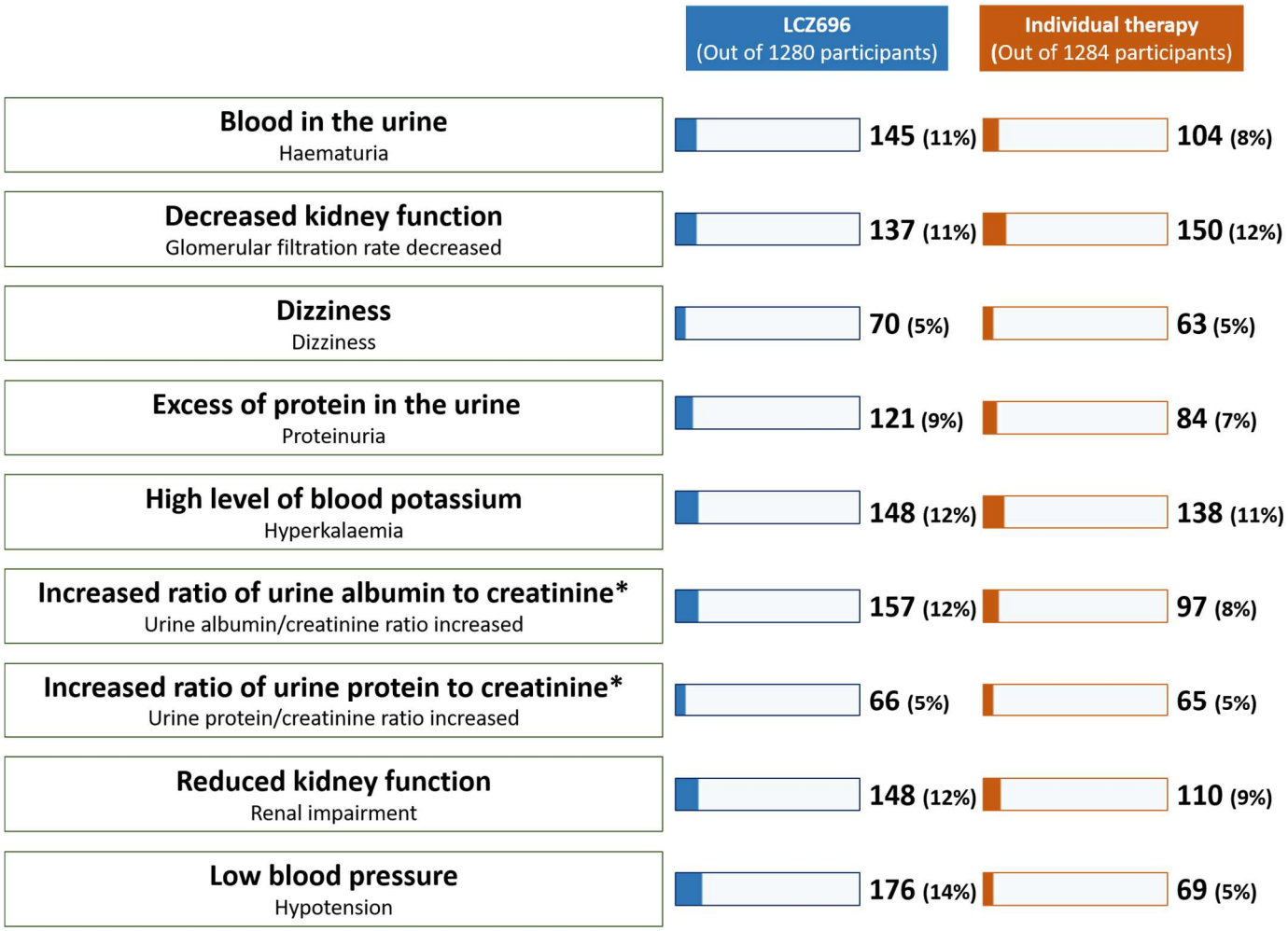
2117 out of 2564 participants (83%) had 1 or more adverse events. During the trial, 214 out of 2564 participants (8%) stopped the drug early because of adverse events. Serious adverse events happened in 377 out of 2564 participants (15%) in the trial. 40 out of 2564 participants (2%) participants died during this trial. The individual therapy group refers to participants taking enalapril or valsartan or placebo.

Number of Participants (%) With Adverse Events

	LCZ696 (Out of 1280 participants)	Individual therapy (Out of 1284 participants)
At least 1 adverse event	1087 (85%)	1030 (80%)
At least 1 serious adverse event	186 (15%)	191 (15%)
Stopped drug due to adverse event	121 (9%)	93 (7%)
Death	23 (2%)	17 (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 below.



*Albumin is a protein made by the liver.

Creatinine is a waste product produced in the muscles from the breakdown of a compound called creatine.

Protein can be found in the urine when the kidneys are not working properly.

What were the most common serious adverse events?

The most common serious adverse events that happened in at least 6 participants in any group are presented below:

	LCZ696 (Out of 1280 participants)	Individual therapy (Out of 1284 participants)
Acute heart failure Cardiac failure acute	3 (0.2%)	9 (0.7%)
Chest pain due to heart disease Angina pectoris	8 (0.6%)	8 (0.6%)
Difficulty in breathing Dyspnoea	1 (0.08%)	6 (0.47%)
Heart failure Cardiac failure	21 (1.6%)	31 (2.4%)
Heart failure caused when the heart muscle doesn't pump enough blood Cardiac failure congestive	2 (0.1%)	7 (0.5%)
Irregular heartbeat Atrial fibrillation	13 (1%)	17 (1.3%)
Kidney injury Acute kidney injury	4 (0.3%)	7 (0.5%)
Low blood pressure Hypotension	6 (0.4%)	2 (0.1%)
Lung infection Pneumonia	13 (1%)	13 (1%)
Sudden chest pain Angina unstable	6 (0.4%)	7 (0.5%)
Stroke caused by abnormal blood vessel Ischaemic stroke	0 (0%)	6 (0.4%)

How many participants stopped trial drug due to adverse events?

During the trial, 121 out of 1280 (9%) of participants stopped LCZ696 early due to adverse events and 93 out of 1284 (7%) participants stopped the individual therapy early due to adverse events.

The most common adverse events that led to stopping the trial treatments early were **low blood pressure** (hypotension), **kidney problem** (renal impairment), and **high level of blood potassium** (hyperkalemia).

How was this trial useful?

This trial helped researchers find out if LCZ696 was safe and if it had beneficial effects on patients with **HF with preserved EF** compared to enalapril and valsartan. Researchers learned that LCZ696 was able to lower the blood levels of **NT-proBNP**. Researchers also found participants in both groups showed a modest improvement in the capacity to walk, however, the difference between the effects of the 2 groups may have been due to chance.

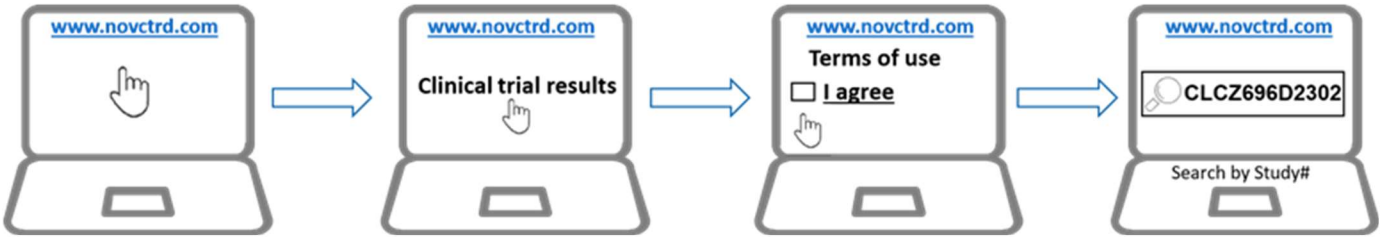
Researchers also found that the adverse events that happened during this trial were common in people with **HF with preserved EF**. LCZ696 reduced the chance of having a serious side effect of heart failure compared with other drugs tested in the trial.

Results from this trial may be used in other clinical trials for people with **HF with preserved EF**.

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).



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

- www.clinicaltrials.gov Use the NCT identifier NCT03066804 in the search field.
- https://www.clinicaltrialsregister.eu/ctr-search/search Use the EudraCT identifier 2016-003410-28 in the search field.

Full clinical trial title: A 24-week, randomized, double-blind, multi-center, parallel group, active controlled study to evaluate the effect of LCZ696 on NT-proBNP, exercise capacity, symptoms and safety compared to individualized medical management of comorbidities in patients with heart failure and preserved ejection fraction

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

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www.novartisclinicaltrials.com