NOVARTIS

Clinical Trial Results Summary

A clinical trial to learn about the effects of LCZ696 compared to valsartan in participants with worsening heart failure

Protocol number: CLCZ696DUS01

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.

Thanks to the participants for taking part in this trial for the drug **sacubitril/valsartan**, also known as **LCZ696**. They helped researchers learn more about how **LCZ696** works in people with heart failure.

?

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

This summary shows the results of a single clinical trial. Other clinical trials may have different findings.

Why was the research needed?

Researchers were looking for a better way to treat **heart failure (HF)**.

Heart failure occurs when the heart is weak and cannot pump enough blood to your lungs and the rest of your body. Chronic heart failure is generally a condition that develops gradually over time.

Ejection fraction (EF) is the amount of blood leaving your heart each time it beats.

Heart failure with preserved ejection fraction (HFpEF) is a long-term condition in which the heart muscle loses its 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. This can lead to common symptoms of heart failure such as shortness of breath, weakness, feeling tired, and swollen ankles and legs, which can be seen even at rest.

LCZ696 (sacubitril/valsartan) is a drug that is currently approved in the US to treat chronic HF, including some people with **HFpEF**, but is approved in Canada only for another form of HF called HF with reduced ejection fraction.

Drug	***Pronounced as***
sacubitril/valsartan	su-KOO-bi-tril/ val-SAR-tan

In this trial, researchers wanted to evaluate the effect of **LCZ696** compared to another drug (**valsartan**) in people with **HFpEF**, who had a **worsening HF event**.

A **worsening HF** event could be:

- a hospitalization, or
- a visit to the emergency department/room, or
- a visit to the doctor,

These events require the use of diuretics to be given as an injection into the veins. Diuretics are medicines which help to remove extra fluid from the body.

How long was this trial?

This trial started in June 2019 and ended in December 2022. It was planned for each participant to be in the trial for a maximum of 20 months.

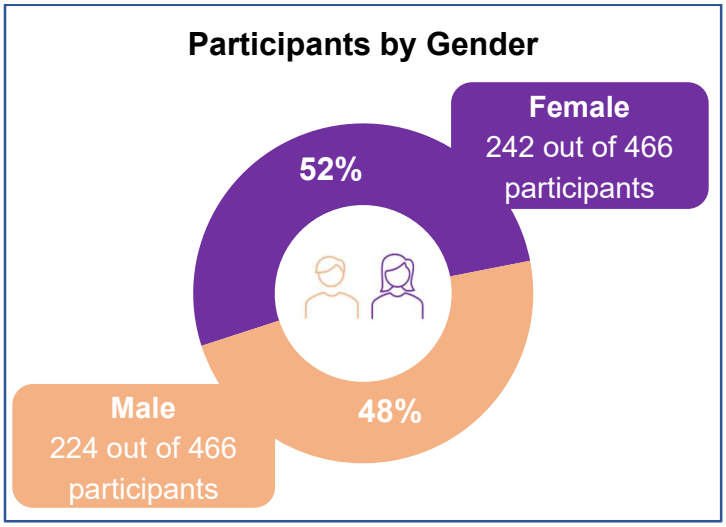
Who was in this trial?

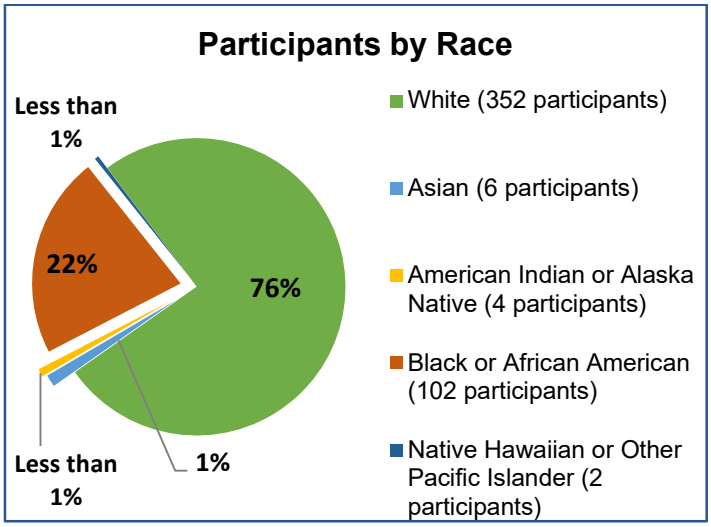
Participants with **HFpEF** could take part in this trial if they:

- were 18 years or older,
- were hospitalized or within 30 days of being discharged following a **worsening HF event**,
- had a high level of N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP). NT-proBNP is a protein produced in large amounts by the heart when it is not working properly, as in HF,
- had not taken a certain group of blood pressure lowering medicines called angiotensin converting enzyme inhibitors for 36 hours before entering the trial.

A total of 466 participants from 2 countries participated in this trial: 423 participants were from the United States and 43 from Canada.

Participants' ages ranged from 27 to 95 years. The average age of the participants was 70 years. Most participants were female (52%) and white (76%).





What treatments did the participants take?

Each participant received 2 tablets (either Trial drug + Placebo or Comparator + Placebo):

Trial drugs		Comparator	
	**LCZ696**, 50 mg or 100 mg or 200 mg tablets, given twice a day by mouth.		**Valsartan**, 40 mg or 80 mg or 160 mg tablets, given twice a day by mouth.
	**Placebo**, which looked like the trial drug, but did not have any medicine in it. As the drugs given in the trial looked different, participants were also given matching placebo along with the trial drugs.		

During the trial, the participants continued to take other medicines for long-term HF and other conditions as prescribed by their doctor.

Participants could take rescue medications if needed. Rescue medications are the medicines given to relieve symptoms of worsening HF immediately.

What happened during this trial?

Before treatment

The trial doctors checked if participants could take part in this trial.

Up to 4 weeks

During treatment

Part 1 (up to 80 weeks):

466 participants were randomly assigned to one of the following 2 treatment groups:

- **LCZ696** 50 mg, 100 mg, or 200 mg **+ Placebo** (233 participants), or

- **Valsartan** 40 mg, 80 mg, or 160 mg **+ Placebo** (233 participants).

Each participant had an equal chance of ending up in either group. None of the participants, trial doctors, or trial staff knew what treatment the participants were receiving.

The doses were increased every 2 weeks based on doctor's judgment. The target dose was then maintained until the end of the trial.

Starting dose	Next higher dose	Target dose
50 mg **LCZ696** + **Placebo** or 40 mg **valsartan** + **Placebo**	100 mg **LCZ696** + **Placebo** or 80 mg **valsartan** + **Placebo**	200 mg **LCZ696** + **Placebo** or 160 mg **valsartan** + **Placebo**

Up to 84 weeks

Part 2 (up to 4 weeks):

Out of 466 participants, 50 entered the follow-up phase during which all 50 participants took **LCZ696** twice a day, for up to 4 weeks. During this phase, researchers and participants knew that the participants were taking **LCZ696**.

After treatment

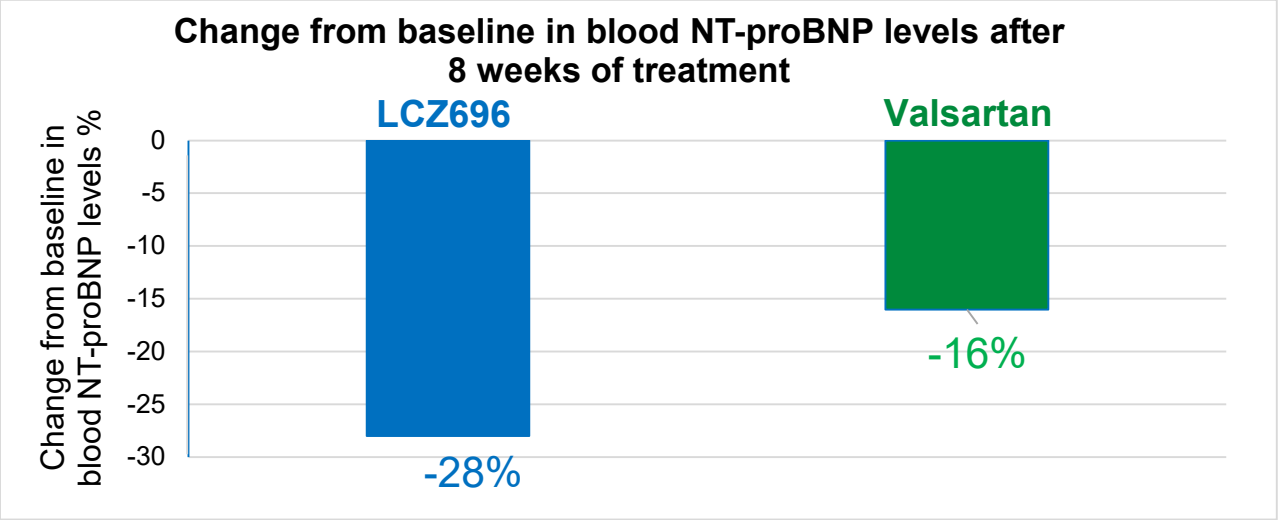
Participants' health was monitored for 4 weeks.

Up to
4 weeks

What were the main results of this trial?

What were the differences in blood NT-proBNP levels after 8 weeks of treatment with LCZ696 versus valsartan?

After 8 weeks of treatment, participants taking **LCZ696** showed greater reduction in NT-proBNP blood levels compared to the **valsartan** group.



NT-proBNP *is a protein produced in large amounts by the heart when it is not working properly, as in heart failure (HF). A reduction in NT-proBNP blood levels indicates that HF is improving.*

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 any 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 that happened in the 2 treatment groups during the trial are listed in the table below.

Number of Participants (%) With Adverse Events

	Part 1		Part 2
	LCZ696 + Placebo (Out of 233 participants)	**Valsartan + Placebo** (Out of 233 participants)	**LCZ696** (Out of 50 participants)
At least 1 adverse event	161 (69%)	165 (71%)	14 (28%)
At least 1 serious adverse event	119 (51%)	117 (50%)	3 (6%)
Stopped trial due to adverse event	4 (2%)	0	7 (14%)
Deaths	18 (8%)	26 (11%)	0 (0%)

How many participants stopped trial drug due to adverse events?

In Part 1, 4 participants out of 233 taking **LCZ696** + **placebo** stopped the trial due to adverse events. None of the participants taking **valsartan** stopped the trial due to adverse events.

In Part 2, 7 participants out of 50 taking **LCZ696** stopped the trial due to adverse events.

What were the most common serious adverse events?

The most common serious adverse events that happened in at least 5% (5 out of 100) of participants in any group are shown below.

Number of Participants (%) With Serious Adverse Events

	Part 1		Part 2
	LCZ696 + Placebo (Out of 233 participants)	Valsartan + Placebo (Out of 233 participants)	LCZ696 (Out of 50 participants)
Worsening heart failure (Cardiac failure)	22 (9%)	20 (9%)	0
Inability of the kidneys to work properly (Acute kidney injury)	21 (9%)	15 (6%)	0
Heart failure (Cardiac failure congestive)	14 (6%)	19 (8%)	0
Low blood pressure (Hypotension)	15 (6%)	13 (6%)	0
Sudden heart failure (Cardiac failure acute)	11 (5%)	14 (6%)	0
Irregular heartbeat (Atrial fibrillation)	10 (4%)	13 (6%)	0
Lung infection (Pneumonia)	7 (3%)	14 (6%)	0

What were the most common other adverse events?

The most common other adverse events that happened in more than 10% (10 out of 100) of participants in any group are presented below.

Number of Participants (%) With Other Adverse Events

	Part 1		Part 2
	LCZ696 + Placebo (Out of 233 participants)	**Valsartan + Placebo** (Out of 233 participants)	**LCZ696** (Out of 50 participants)
Low blood pressure (Hypotension)	58 (25%)	40 (17%)	1 (2%)
High levels of potassium in the blood (Hyperkalemia)	38 (16%)	43 (18%)	3 (6%)
Inability of the kidneys to work properly (Acute kidney injury)	35 (15%)	47 (20%)	0 (0%)
Increase of a blood protein called creatinine (Blood creatinine increased)	23 (10%)	27 (12%)	3 (6%)

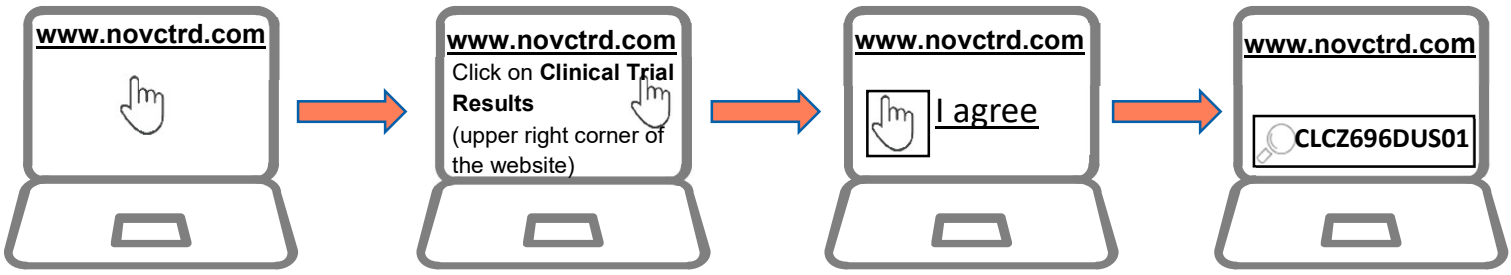
How was this trial useful?

This study helped researchers to learn about the effects and safety of **LCZ696** compared to **valsartan** in patients with **HFpEF** who had a recent worsening heart failure event. Researchers learned that participants who took **LCZ696** showed a greater reduction in NT-proBNP blood levels compared to participants who took **valsartan**. Also, participants who took **LCZ696** had fewer adverse events related to the heart and kidney but a higher number of low blood pressure events than patients taking **valsartan**. Currently, Novartis has no plans for future trials with **LCZ696**.

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**.

Please follow the steps below:



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

- www.clinicaltrials.gov Use the NCT identifier NCT03988634 in the search field.

Full clinical trial title: A multicenter, randomized, double-blind, double dummy, parallel group, active-controlled study to evaluate the effect of sacubitril/valsartan (LCZ696) versus valsartan on changes in NT-proBNP, safety, and tolerability in HFpEF patients with a WHF event (HFpEF decompensation) who have been stabilized and initiated at the time of or within 30 days post-decompensation (PARAGLIDE-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