Clinical Trial Results

NOVARTIS

Research sponsor: Novartis Pharmaceuticals Corporation

Drug studied: sacubitril/valsartan, also called LCZ696

Protocol number: CLCZ696BUS08 (EVALUATE-HF)

Short title: A study to learn how LCZ696 affects aortic stiffness in patients with heart failure with reduced ejection fraction (HFrEF)

Thank You!

Thank you for taking part in the trial to learn if trial drug LCZ696 (sacubitril/valsartan) affects aortic stiffness in people with heart failure. Aortic stiffness occurs when arteries lose elasticity or become "stiff" due to the normal aging process, high blood pressure, and heart disease. This makes the heart work harder and can cause significant health problems. You and all of the other participants helped researchers learn if the trial drug LCZ696, a standard heart failure drug, had any affect on aortic stiffness when compared to another standard heart failure drug.

This summary of the trial results was prepared to provide you with information on what researchers learned from the trial and to acknowledge the important role you played. If you have questions about the results, please speak with the doctor or staff at your trial site.

How long was this trial?

The trial started in August 2016 and ended in January 2019. Your participation in the trial lasted no longer than 30 weeks from the time you signed the informed consent until the end of the trial.

At the end of the trial, the sponsor looked at the data collected and put together the overall results. This is a summary of those results.

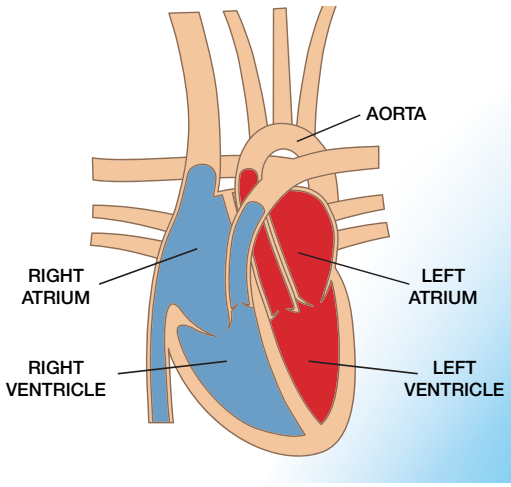
Why was the research needed?

Trial drug LCZ696 treats patients with a type of chronic heart failure where the heart is weak and cannot pump enough blood. Researchers are always looking for better ways to treat heart failure and its symptoms. This trial was done to evaluate how the trial drug LCZ696, compared to another drug (enalapril), affects aortic stiffness among participants.

What is aortic stiffness?
The aorta is the main artery that delivers oxygen-rich blood and nutrients from the heart to all vital organs in the body, and to the arms and legs.

Arteries lose elasticity or become "stiff" due to the normal aging process, high blood pressure, and heart disease. This makes the heart work harder and can cause significant health problems.

Aortic stiffness is measured by ultrasound.



Trial Drugs

The approved, standard heart failure drugs compared in this trial were:

- Trial drug LCZ696 (sacubitril/valsartan)
- Comparator drug enalapril

All of the treatments in this trial were taken as a tablet by mouth.

Trial Purpose

In this trial, researchers compared trial drug LCZ696 to enalapril to answer the following questions:

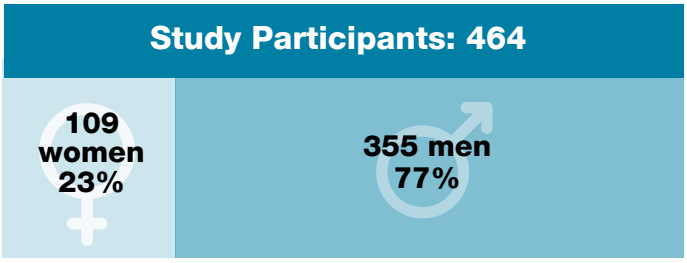
- How does the trial drug LCZ696 affect aortic stiffness (stiffness of the main artery from the heart)?
- Were there any safety concerns (side effects) for each drug?

Who was in this trial?

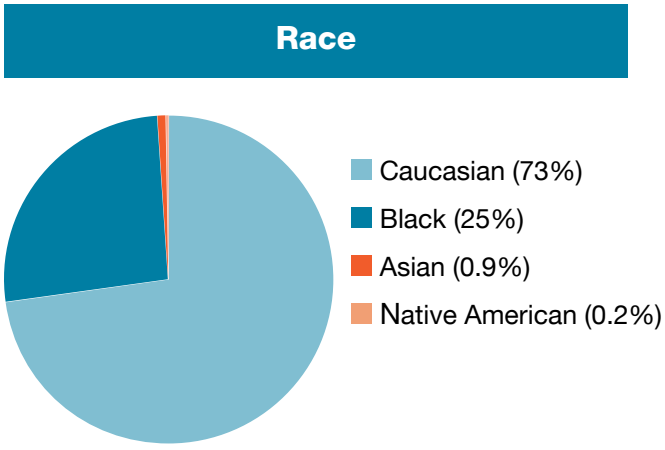
Men and women, like you, with heart failure were asked to participate. Participants ranged in age from 50 to 93. The trial included 464 participants at 85 trial sites in the United States. Out of 464 participants, 355 (77%) were men and 109 (23%) were women.

A majority of participants (341, 73%) identified their race as Caucasian, 115 (25%) identified as Black, 4 participants (0.9%) were Asian and 1 participant identified as Native American. In addition, 310 participants (67%) identified their ethnicity as non-Hispanic/Latino and 152 participants (33%) identified their ethnicity as Hispanic/Latino.

The figures below show who participated in the trial.



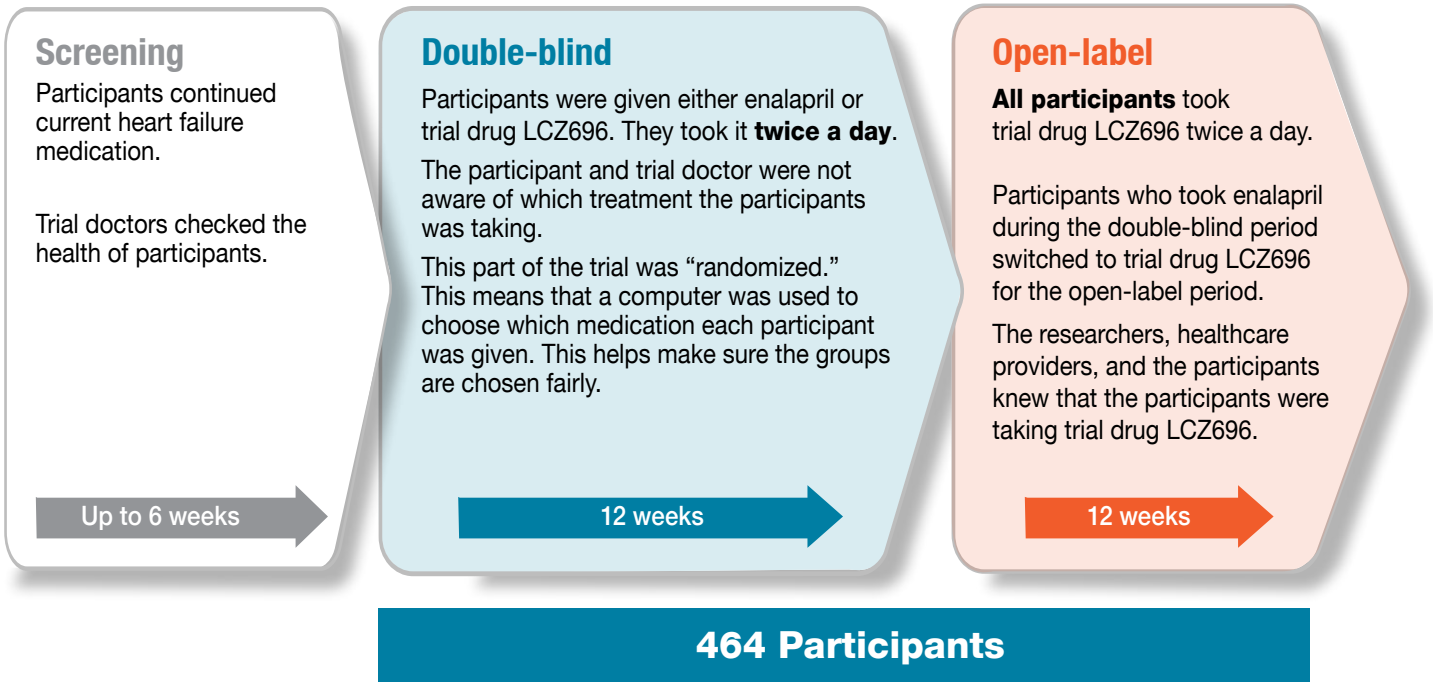
Age Range: 50 - 93 years



Non-Hispanic/Latino	(67%)
Hispanic/Latino	(33%)

How was this trial done?

The figure below shows the three periods of the trial.



What were the results of the trial?

This is a summary of the overall results of this trial. Both drugs (enalapril and trial drug LCZ696) are approved and effective for the treatment of heart failure, but neither drug had a meaningful impact on aortic stiffness.

The trial answered the following questions:	
Question	**Answer**
How does the trial drug change aortic stiffness after 12 weeks of treatment with trial drug LCZ696 versus enalapril?	There was no reduction in aortic stiffness for participants taking trial drug LCZ696 or those taking enalapril. Therefore, the trial failed to show that trial drug LCZ696 was effective at reducing aortic stiffness.
Were there any safety concerns (side effects) for each drug?	No new safety concerns were identified.

What medical problems did the participants have?

Medical problems that happen in clinical trials are called “adverse events”. An adverse event is any unwanted sign or symptom that participants have during a trial. An adverse event is considered “serious” when it is life-threatening, causes lasting problems or requires hospital care.

This trial showed that LCZ696 is generally safe and well tolerated. Adverse events reported in this trial were the same as what is normally seen in patients with heart failure.

What were the most common adverse events in this trial?

The following table demonstrates the adverse events reported by at least 5% of the participants.

The most frequent adverse events participants reported during the trial was low blood pressure (hypotension) and increased blood potassium (hyperkalemia). Although dizziness was reported at a lower percent than hypotension, it can be associated with hypotension as hypotension can cause dizziness. The same adverse events were reported in the open-label period when all participants received trial drug LCZ696 but were reported at a lower rate.

A participant could have experienced more than one adverse event, therefore the total adverse events in the chart below includes participants who may have experienced more than one adverse event. Adverse events reported in this trial were the same as what has been reported in patients with heart failure.

Most Common Adverse Events in Double-blind Period of Trial		
Adverse Events reported in at least 5% of any group	Enalapril out of 233 participants	LCZ696 out of 231 participants
Total Number of Affected Participants*	32 (13.7%)	43 (18.6%)
Increased blood potassium (Hyperkalemia)	13 (5.6%)	17 (7.4%)
Dizziness	9 (3.9%)	13 (5.6%)
Decrease in blood pressure (Hypotension)	13 (5.6%)	19 (8.2%)

Most Common Adverse Events in Open-label Period of Trial	
Adverse Events reported in at least 5% of any group	All Participants took trial LCZ696 out of 454 participants
Total Number of Affected Participants*	42 (9.3%)
Increased blood potassium (Hyperkalemia)	12 (2.6%)
Dizziness	15 (3.3%)
Decrease in blood pressure (Hypotension)	16 (3.5%)

*Participants could have experienced more that than one adverse event.

How many participants had serious adverse events?

There were serious adverse events that occurred during the trial. These were not necessarily related to the trial drug. The primary cause of death for the 7 participants who died during the study or 30-day follow-up was cardiovascular-related for 6 participants and non-cardiovascular for 1 participant.

Serious Adverse Events in Double-blind Period of Trial		
Adverse Events reported in at least 5% of any group	Enalapril out of 233 participants	LCZ696 out of 231 participants
Total Number of Affected Participants	21 (9.0%)	17 (7.4%)
Deaths	1 (0.4%)	1 (0.4%)

Serious Adverse Events in Open-label Period of Trial	
(all 454 participants took trial drug LCZ696)	
Total Number of Affected Participant	40 (8.8%)
Deaths	5 (1.1%)

How was this trial useful?

The trial helped researchers learn that the trial drug LCZ696 compared with enalapril in participants with heart failure did not reduce aortic stiffness. The safety findings in this trial were similar to what researchers have seen in other trials of LCZ696.

Please remember, this summary only shows the results of a single clinical trial. Other clinical trials may have different results. Researchers and health authorities 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. Always talk to a doctor before making any changes to medications or treatment plans.

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). Once on the site, click “Clinical trial results” at the bottom of the page. After agreeing to enter the Novartis website, type CLCZ696BUS08 into the search by trial number box and click “Search”.

You can find more results of this trial on the following website:
www.clinicaltrials.gov. Use the NCT identifier NCT02874794 in the search field.

Full Clinical Trial Title: A Multicenter, Randomized, Double-blind, Double-dummy, Parallel Group, Active-controlled, Forced-titration, 12-week Comparison of Combined Angiotensin-neprilysin Inhibition With Sacubitril and Valsartan Versus Enalapril on Changes in Central Aortic Stiffness in Patients With Heart Failure and 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 participants around the world. You helped researchers answer important health questions and test new medical treatments.

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