Clinical Trial Results

NOVARTIS

Research sponsor: Novartis Pharmaceuticals Corporation

Drug studied: sacubitril/valsartan, also called LCZ696

Protocol number: CLCZ696BUS01 (PIONEER-HF)

Short title: A study to learn how LCZ696 impacts heart failure when given in the hospital

Thank You!

Thank you for taking part in the trial to learn how the trial drug, sacubitril/valsartan, also called LCZ696, impacts heart failure when given in the hospital. You and all of the other participants helped researchers learn more about LCZ696 and how to treat patients with heart failure.

This summary of trial results was prepared to provide you with information about 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 April 2016 and ended in July 2018. You could have been in the trial for about 12 weeks from the time you signed the informed consent until the end of the trial. However, the entire trial took about 27 months to finish.

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 was originally approved by the FDA to treat patients with chronic heart failure in July 2015. This trial was done to evaluate how LCZ696 compares to another drug (enalapril) among participants who were hospitalized with worsening heart failure. Researchers are always looking for better ways to treat heart failure and its symptoms.

Trial Drugs

The drugs compared in this trial were:

- Trial drug LCZ696 (sacubitril/valsartan)
- Comparator drug enalapril (a drug that is a standard heart failure treatment)

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

Trial Purpose

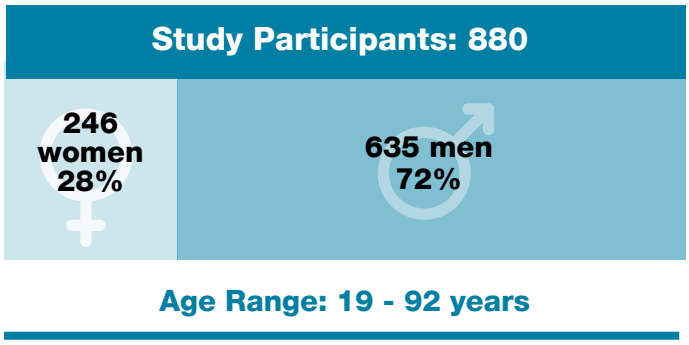
In this trial, researchers compared trial drug LCZ696 to enalapril to answer these specific questions for patients hospitalized with worsening heart failure:

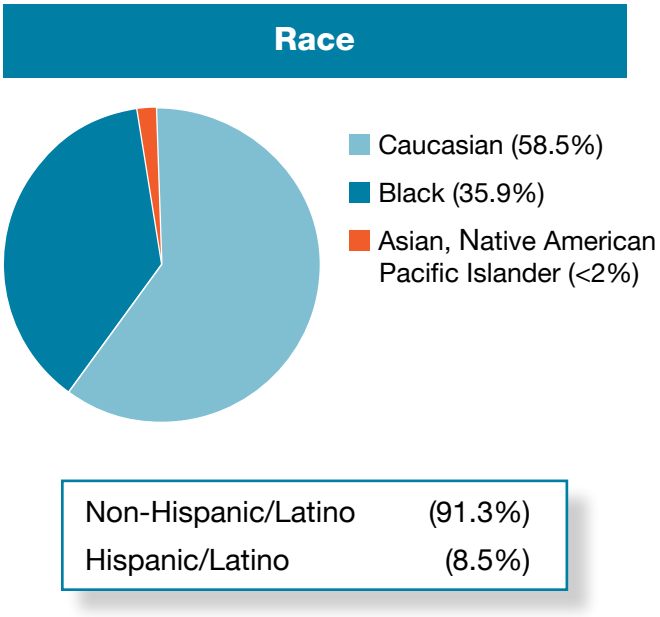
- What are the differences in blood “biomarkers” (indicate if heart failure is improving) after 8 weeks of treatment with LCZ696 versus enalapril?
- What if any differences are there in safety concerns (adverse events) for each drug when they were started in the hospital?

Who was in this trial?

Men and women, who were hospitalized due to their heart failure, were asked to participate. Participants ranged in age from 19 to 92. The trial included 881 participants at 133 trial sites in the United States. Out of 881 participants, 246 (28%) were women and 635 (72%) were men. There were 515 participants (58.5%) that identified their race as Caucasian and 316 participants (35.9%) identified their race as Black. Other groups represented less than 2% of participants and included; Asian, Native American and Pacific Islander ethnicities. In addition, 804 participants (91.3%) identified their ethnicity as non Hispanic/Latino and 75 participants (8.5%) identified their ethnicity as Hispanic/Latino.

The figures below show who participated in the trial.

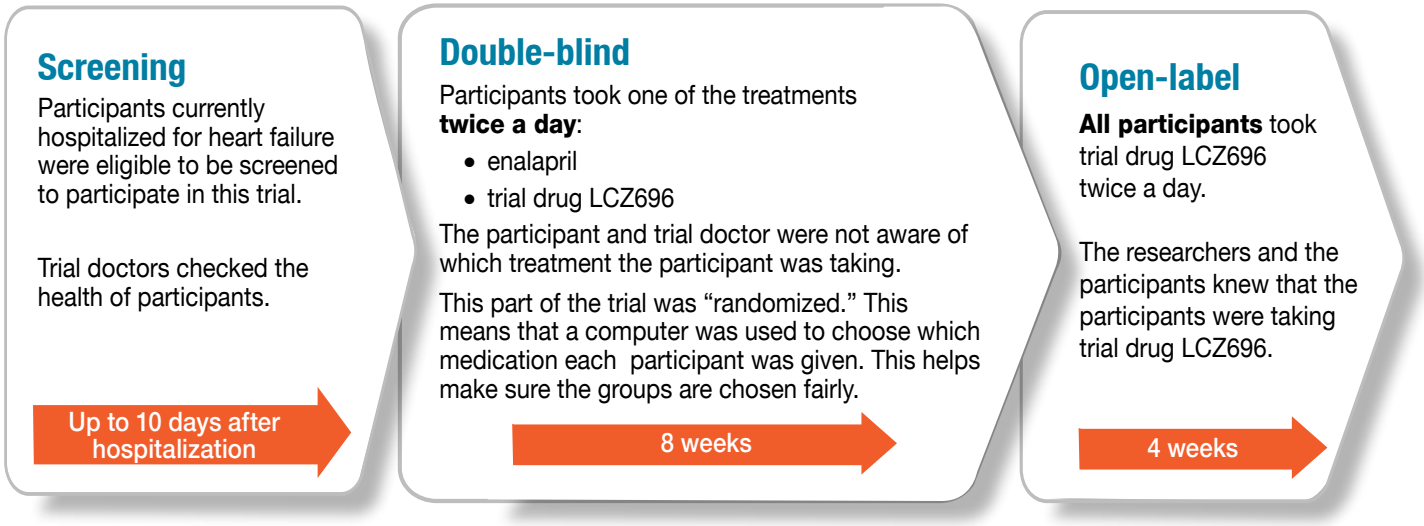




How was this trial done?

The figure below shows the three periods of the trial.

A Double-blind and Open-label trial: 881 Participants



What were the results of the trial?

This is a summary of the overall results of this trial. The individual results of each participant might be different and are not in this summary. Other trials may provide new information or different results. Medical decisions should not be made based on the results of a single trial without first talking to a doctor. Always talk to a doctor before making any change to medications or treatment plans.

The trial answered the following questions:	
Question	**Answer**
What are the differences in blood "biomarkers" (indicate if heart failure is improving) after 8 weeks of treatment with LCZ696 versus enalapril?	Participants treated with LCZ696 showed improvement of the elevated biomarker compared to enalapril at the end of the 8 week trial.
What if any differences are there in safety concerns (side effects) for each drug when they were started in the hospital?	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 had during the trial. An adverse event is considered "serious" when it is life-threatening, causes lasting problems or requires hospital care.

This trial showed that trial drug LCZ696 is generally safe and well tolerated. Adverse events reported in this trial were the same as what is normally seen in this patient population.

How many participants had serious adverse events?

Re-hospitalization was the most common reason for a serious adverse event in the double-blind and open-label period of the trial. The most commonly reported serious adverse events included; acute kidney injury, cardiac failure, and hypotension. Overall, the rate of participants experiencing death, heart failure, re-hospitalization, requirement of a ventricular assist device or listing for cardiac transplantation was lower in participants taking trial drug LCZ696.

There were 31 total deaths reported in the trial. The breakdown was as follows: 15 participants from the double-blind period randomized to enalapril and 10 participants randomized to trial drug LCZ696. There were 6 deaths in the open-label period.

Information on the outcomes associated with a serious adverse event were collected throughout the double-blind and open-label period of the trial but information was only analyzed for the double-blind period. The table below shows a breakdown of the number of participants in the double-blind period with the most serious result due to a serious adverse event. Results collected included; death, re-hospitalization, requirement of a ventricular assist device or cardiac transplantation.

Results Collected in Enalapril and LCZ696 Participants		
Result Associated with Serious Adverse Event*	**Enalapril Participants Affected out of 436 participants**	**LCZ696 Participants Affected out of 439 participants**
Death	15 (3.4%)	10 (2.4%)
Heart failure re-hospitalization (hospital stay ≥24 hours)	61 (13.8%)	35 (8.0%)
Requirement of a ventricular assist device	1 (0.2%)	1 (0.2%)
Cardiac transplantation	0	0

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

What were the most common adverse events in this trial?

The most common adverse event participants or the trial doctors reported during the trial was hypotension, a decrease in blood pressure. The patient may have had a drop in blood pressure, but not all drops in blood pressure cause a patient to have symptoms, such as dizziness.

The following table shows the most common adverse events reported at least 5% of the time in either the double-blind or the open-label period of the trial.

A total of 40.4% of participants randomized to enalapril and 41.9% of participants randomized to trial drug LCZ696 had reported adverse events that occurred at least 5% of the time.

As an example, the most common adverse event reported in participants taking enalapril was hypotension and was reported 79 times. This is the same number of reports for hypotension in participants taking trial drug LCZ696.

Most Common Adverse Events in Double-blind Period of Trial*		
Adverse Event reported in at least 5% of any group	**enalapril out of 436 participants**	**LCZ696 out of 439 participants**
Total Number of Affected Participants	**176 (40.4%)**	**184 (41.9%)**
Decrease in blood pressure (hypotension)	79 (18.1%)	79 (18%)
Increased blood potassium (hyperkalaemia)	40 (9.2%)	55 (12.5%)
Abrupt loss of kidney function (acute kidney injury)	37 (8.5%)	36 (8.2%)
Dizziness	33 (7.6%)	39 (8.9%)
Cardiac failure congestive (heart failure that prompts you to go to ER or seek urged treatment)	32 (7.3%)	22 (5.0%)
Blood creatinine increase	19 (4.4%)	31 (7.1%)

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

Most Common Adverse Events in Open-label Period of Trial (all 828 participants took trial drug LCZ696)*	
Adverse Event reported in at least 5% of any group	**LCZ696 Participants Affected**
Total Number of Affected Participants	93 (11.2%)
Decrease in blood pressure (hypotension)	44 (5.3%)
Dizziness	21 (2.5%)
Cardiac failure congestive (heart failure that prompts you to go to ER or seek urged treatment)	16 (1.9%)
Increased blood potassium (hyperkalaemia)	15 (1.8%)
Acute kidney injury (abrupt loss of kidney function)	8 (1.0%)
Impaired kidney function (increase in blood creatinine)	7 (0.8%)

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

How was this trial useful?

The trial helped researchers learn how LCZ696 impacts a measurement of a biomarker in the blood when initiated in the hospital setting compared to enalapril. This trial also helped researchers learn how safe LCZ696 is compared to enalapril when initiated in the hospital setting, including the impact on hospitalizations, death, need for heart transplantation or need for a left ventricular assist device.

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.

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, select “Search By Study Number”, then type CLCZ696BUS01 into the keyword search box and click “Search”.

You also can find more information about this trial on the following website: www.clinicaltrials.gov. Use the NCT identifier NCT02554890 in the search field.

Full Clinical Trial Title: Comparison of Sacubitril/Valsartan Versus Enalapril on Effect on NT-proBNP in Patients Stabilized From an Acute Heart Failure Episode. (PIONEER-HF)

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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