Clinical Trial Results

NOVARTIS

Research sponsor:	Novartis Pharmaceuticals Corporation
Drug studied:	sacubitril/valsartan, also called LCZ696
Protocol number:	CLCZ696BUS14 (AWAKE-HF)
Short title:	A study to learn how LCZ696 impacts waking activity and sleep

Thank You!

Thank you for taking part in the trial to learn if the trial drug sacubitril/valsartan, also called LCZ696, could increase daytime activity and improve restful sleep at night. You and all of the other participants helped researchers learn more about trial drug LCZ696 and how to treat patients with heart failure.

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 in this trial. 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 December 2016 and ended in March 2018. You could have been in the trial for about 18 weeks from the time you signed the informed consent until the end of the trial. However, the entire trial took about 15 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 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 trial drug LCZ696 affects daytime activity and nighttime sleep in participants with heart failure.

Trial Drugs

The drugs compared in this trial were:

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

Trial Purpose

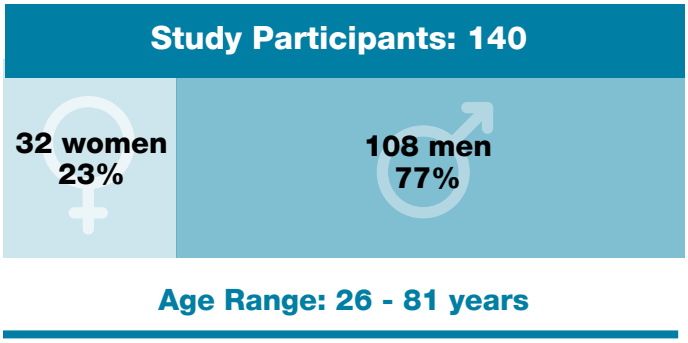
In this trial, the main unanswered questions researchers wanted to try to answer were:

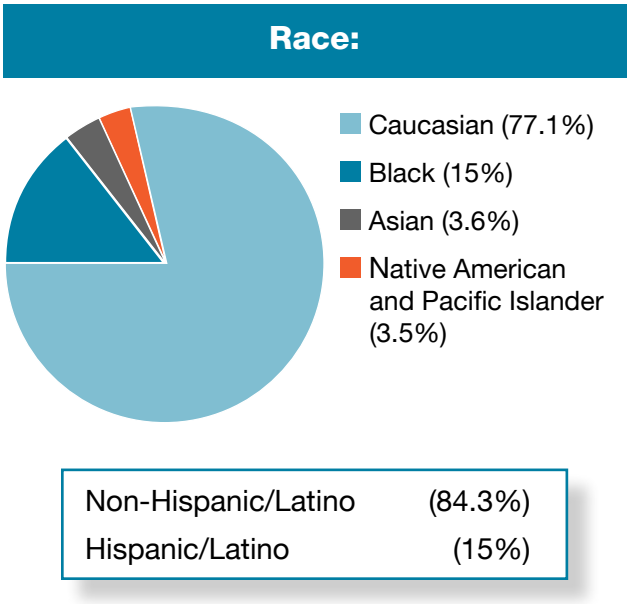
- Was there a difference between the trial drug LCZ696 compared to enalapril on physical activity levels during the day?
- Was there a difference between the trial drug LCZ696 compared to enalapril on sleep during the night?

Who was in this trial?

Men and women, like you, with heart failure were asked to participate. Participants ranged in age from 26 to 81. The trial included 140 participants at 23 trial sites in the United States. Out of 140 participants, 32 (23%) were women and 108 (77%) were men. A majority of participants (106, 77.1%) identified their race as Caucasian and 21 participants (15.0%) identified their race as Black. Other groups represented included; Asian (3.6%), Native American and Pacific Islander represented less than 3.5% of participants. In addition, 118 participants (84.3%) identified their ethnicity as non-Hispanic/Latino and 21 participants (15.0%) identified their ethnicity as Hispanic/Latino.

The figures below show who participated in the trial.





To determine eligibility, participants were asked to sign consent to participate in the trial. The trial doctors then did a physical exam and tests to check the health of the participant. All trial participants were asked about their medical history, how they were feeling, and what medicines they were taking.

If they qualified, each participant was in this trial for about 18 weeks. They visited the trial site 8 times and had 5 check-ins with their trial center by phone.

What kind of trial was this?

This trial was done in 3 periods: Screening, Double-blind, and Open-label.

During the 2 week screening period, participants continued on their normal heart failure medications and learned how to wear the special watch that measured their activity and how well they slept at night.

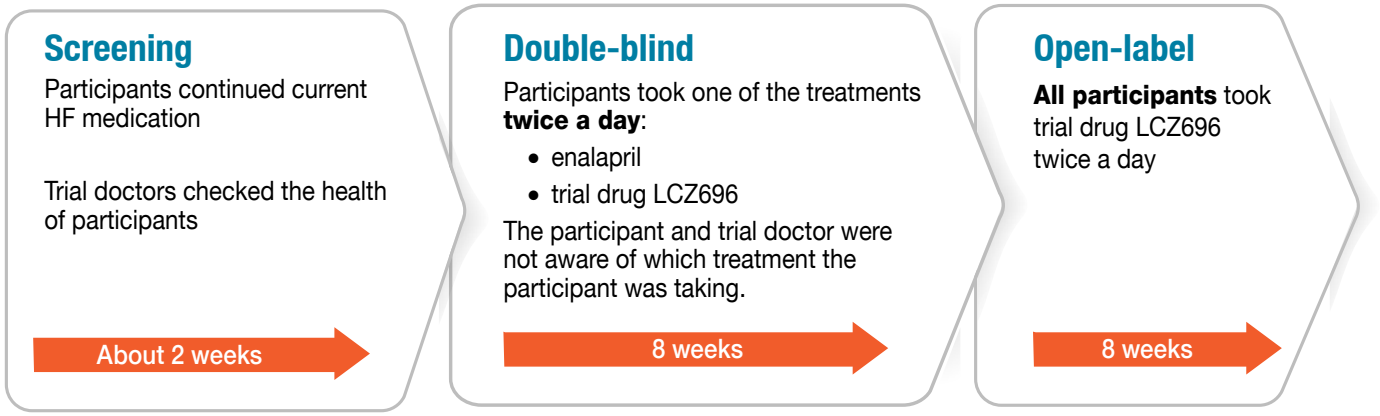
During the double-blind period, none of the participants, trial doctors, or trial staff knew what treatment participants were receiving for the first 8 weeks of the trial. All participants received a medication that has been approved by the FDA to help participants with heart failure.

During the open-label period, the researchers and the participants knew what the participants were taking.

What happened during this trial?

The figure below shows the three periods of the trial.

A Double-blind and Open-label trial: 140 participants



Note: One participant ended participation before taking the study treatment. Therefore of the 140 participants, only 139 participants took either enalapril or LCZ696.

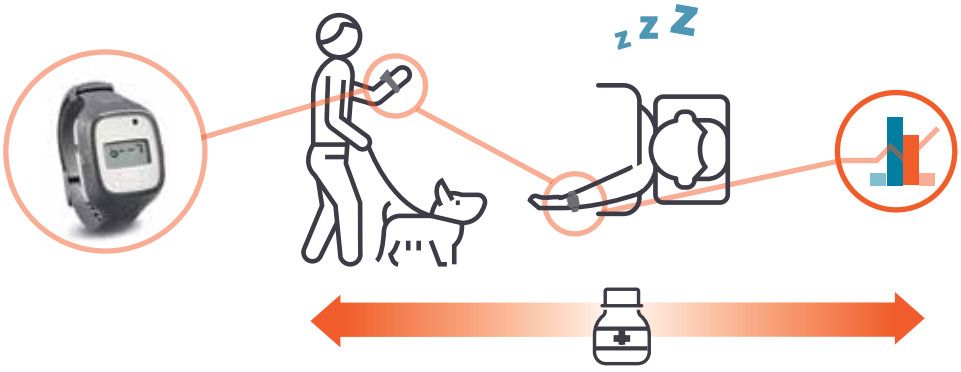
During the screening period, before the treatment started, the trial doctors did tests to make sure participants could take part in the trial. The participants:

- Had a physical examination
- Had laboratory tests
- Had a urine pregnancy test (if female)
- Reviewed their medications with the trial team
- Reviewed the informed consent with the trial team to ensure understanding of the trial

During the double-blind period, 70 participants were given trial drug LCZ696 and 70 participants were given enalapril. This part of the trial was "**randomized**." This means that a computer was used to choose which medication each participant was given. This helps make sure the groups are chosen fairly. This part of the trial lasted 8 weeks.

During the open-label period, all participants who completed the double-blind period were given the trial drug LCZ696. At this time, the trial became "open-label." This means the researchers and the participants knew what the participants were taking. This part of the trial lasted 8 weeks.

A special wristwatch worn by each participant measured both physical activity and sleep. The watch recorded each person's most active 30 minutes of the day. The wristwatch also measured how much restful sleep each person had at night.



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**
Do participants taking LCZ696 have a change in their physical activity during the day compared to enalapril?	Participants treated with LCZ696 showed no change in physical activity during the day compared to enalapril.
Do participants taking LCZ696 have more restful sleep at night compared to enalapril?	Participants treated with LCZ696 showed no improvement in how well participants slept at night compared to enalapril.

What medical problems did the participants have?

Medical problems that happen in a clinical trial 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 leads to hospitalization.

During a trial, researchers keep a record of all medical problems participants have to determine whether or not they are caused by the trial drug. This is a summary of medical problems that happened in this trial. A lot of research is needed to know whether the trial drug caused a medical problem and how safe it is for patients.

The trial showed that trial drug LCZ696 is generally safe and well tolerated. Adverse events reported in this trial were the same as what has been previously reported in this patient population on these medications.

How many participants had serious adverse events?

Serious adverse events were infrequent in the trial. There was one death due to a stroke of a participant during the trial who was taking enalapril in the double-blind period of the trial.

The tables below show the breakdown of the number of participants with a serious adverse event in each treatment group.

Serious Adverse Events in Double-blind Period of Trial	
Enalapril Participants Affected out of 70 participants	**LCZ696 Participants Affected out of 69 participants**
4 (5.7%)	5 (7.2%)

Serious Adverse Events in Open-label Period of Trial Open-label (all participants took trial drug LCZ696)	
Enalapril Participants in Double-blind Who Took Trial Drug LCZ696 in Open-label Affected (out of 62 participants)	**LCZ696 Participants in Double-blind Who Took Trial Drug LCZ696 in Open-label Affected (out of 64 participants)**
4 (6.5%)	3 (4.7%)

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 in either the double-blind or the open-label periods of the trial. (5 out of 100 in any treatment group)

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.

The following table shows the most common adverse events, and number of participants who experienced a specific adverse event.

Most Common Adverse Events in Double-blind Period of Trial

Adverse Event reported in at least 5% of any group	Enalapril out of 70 participants	LCZ696 out of 69 participants
Total Number of Affected Participants	**27 (38.6%)**	**9 (13.0%)**
Dizziness	12 (17.1%)	5 (7.2%)
Tiredness	9 (12.9%)	1 (1.4%)
Diarrhea	6 (8.6%)	1 (1.4%)
Decrease in Blood Pressure	4 (5.7%)	1 (1.4%)
Vomiting	4 (5.7%)	0 (0.0%)
Urinary Tract Infection**	1 (1.4%)	1 (1.4%)
TOTAL NUMBER OF ADVERSE EVENTS	**36***	**9***

*Participants could have experienced more that than one adverse event.
**Urinary tract infection included in Double-blind for your comparison since there were at least 5% in Open-label (see next table).

Most Common Adverse Events in Open-label Period of Trial (all participants took trial drug LCZ696)

Adverse Event reported in at least 5% of any group	Enalapril Participants in Double-blind Who Took Trial Drug LCZ696 in Open-label Period Out of 62 participants	LCZ696 Participants in Double-blind Who Took Trial Drug LCZ696 in Open-label Period out of 64 participants
Total Number of Affected Participants	13 (21.0%)	11 (17.2%)
Dizziness	5 (8.1%)	4 (6.3%)
Tiredness	1 (1.6%)	5 (7.8%)
Decrease in Blood Pressure	4 (6.5%)	4 (6.3%)
Urinary tract infection	4 (6.5%)	1 (1.6%)
Diarrhea**	2 (3.2%)	1 (1.6%)
Vomiting**	1 (1.6%)	0 (0.0%)
TOTAL NUMBER of ADVERSE EVENTS*	**17***	**15***

*Participants could have experienced more that than one adverse event.
** Diarrhea and vomiting included in Open-label for your comparison since there were at least 5% of both events in Double-blind (see table above).

How was this trial useful?

The trial helped researchers learn how LCZ696 impacts daytime activity compared to enalapril. It also helped researchers understand how LCZ696 impacts restful sleep at night compared to enalapril. The trial results showed no difference between the two trial drugs on physical activity during the day or how well participants slept at night. This trial helped researchers to learn that the safety findings in this trial were similar to what we have seen in other trials of LCZ696 compared to enalapril.

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 availabel 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 CLCZ696BUS14 into the keyword search box and click “Search”.

You can find more information about this trial on the following website: www.clinicaltrials.gov. Use the NCT identifier NCT02970669 in the search field.

Full Clinical Trial Title: Study on the Effects of Sacubitril/Valsartan on Physical Activity and Sleep in Heart Failure With Reduced Ejection Fraction Participants. (AWAKE-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 who help researchers answer important health questions and test new medical treatments.

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1-888-669-6682 (US)
+41613241111 (EU)
www.novartisclinicaltrials.com