NOVARTIS

Clinical Trial Results Summary

A clinical trial to learn more about the effects of LCZ696/ARNI on irregular heart rhythm in Chinese people with heart failure who have a pacemaker

Thank you!

Thank you to the participants who took part in the clinical trial for heart failure. Every participant helped the researchers learn more about the trial drug **LCZ696/ARNI**, also called **Sacubitril/Valsartan**.

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. We hope this helps the participants understand their important role in medical research.

Trial information

Trial number: CLCZ696BCN04

Drug studied: **LCZ696** also known as **LCZ696/ARNI**, or **Sacubitril/Valsartan**

Sponsor: Novartis

If you were a participant and have any questions about the results, please talk to the doctor or staff at the trial site.

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

What was the main purpose of this trial?

The purpose of this trial was to learn about the effects of **LCZ696/ARNI** on irregular heart rhythm in Chinese participants with heart failure, who had a pacemaker in their bodies to regulate their heartbeat.

To find this out, researchers compared the effects of treatment with **LCZ696/ARNI** on irregular heart rhythms with two other treatments called **angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) (ACEI/ARB)**. **LCZ696** is a medicine which belongs to the treatment called **angiotensin receptor nephrilysin inhibitor (ARNI)**. In this document, the trial drug is called as **LCZ696/ARNI**.

Participants included in this trial had heart failure with reduced ejection fraction (HFrEF).

People with HFrEF have trouble doing daily physical activities and exercise. They are also more likely to have irregular heart rhythm. To treat irregular heart rhythm, doctors put a device in their body, called pacemaker. If an irregular heart rhythm is detected, the pacemaker delivers a small electric shock to restore the normal heart rhythm.

Results from an earlier trial done in small number of people with HFrEF who had a pacemaker, showed that **ARNI** can help decrease the events of irregular heart rhythms.

What is HFrEF?

HFrEF 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. It causes the common symptoms of heart failure, such as shortness of breath, weakness, feeling tired, and swollen ankles and legs.

The researchers noticed that not much is known about the effects of treatment with **LCZ696/ARNI** and **ACEI/ARB** on irregular heart rhythm in Chinese people with HFrEF who already had a pacemaker.

LCZ696/ARNI includes 2 medicines in it, sacubitril and valsartan. It is approved for the treatment of HFrEF. It helps the heart to pump blood properly and to control irregular rhythms.

Angiotensin-converting enzyme inhibitor/ angiotensin receptor blockers (ACEI/ARB) are two types of treatment. They are standard treatments to treat heart failure. ARBs are advised for those who cannot tolerate ACEI treatment.

Trial drug
LCZ696/ARNI
also called
Sacubitril/Valsartan
Pronounced as
sak-UE-bi-tril/
val-SAR-tan

The trial purpose was to answer these main questions:

- How many participants had irregular heart rhythm events during 6 months of **LCZ696/ARNI** treatment compared to 6 months of **ACEI/ARB** treatment?
- What adverse events did the participants have during this trial?
  - ↳ An **adverse event** is any sign or symptom that participants have during a trial.

How long was this trial?

The trial began in November 2020 and ended in June 2023. It was planned for the participants to be in the trial for about 1 year and 1 month after receiving the trial treatment.

The sponsor decided to end the trial earlier than planned. This was not due to any safety reasons.

Who was in this trial?

201 Chinese participants with heart failure received treatment in this trial. Participants' ages ranged from 23 to 78 years. Their average age was 61 years. The number of participants by gender are shown below.

Gender

160 Men	41 Women

The participants could take part in this trial if:

- they were between 18 and 80 years of age,
- their heart failed to pump enough blood with each beat,
- they had a pacemaker placed in their body within 2 weeks of start of the trial,
- they had difficulty performing physical activities or were unable to do so without discomfort, and
- they did not have any allergies to any of the trial treatment.

What treatments did the participants receive?

The treatments in this trial were:

Participants took **LCZ696/ARNI** as tablets, by mouth. The trial doctor decided the starting dose. It was based on the dose of **ACEI/ARB** that the participant had received earlier in the trial. The dose could be increased up to a maximum of 200 mg twice a day.

Participants received either **ACEI** or **ARB** taken as tablets or capsules, by mouth. Doses were recommended by the trial doctors and could be increased to the maximum dose a participant could tolerate.

ACEI/ARB were comparators in this trial. A comparator can be an existing marketed product, used as a reference in a trial to compare the effects of the trial treatment.

In this trial all the participants and clinical trial team knew what treatment each participant took. In this trial, all participants first took either **ACEI** or **ARB**, and then later took **LCZ696/ARNI**.

What happened during this trial?

Before treatment — 1 day

Trial doctors checked the health condition and heart function of the participants to make sure they could be in the trial.

During treatment — 1 year

The trial had 2 parts, each part was of 6 months.

Part 1 (First 6 months)

- 201 participants received either **ACEI** or **ARB** for 6 months.
- Participants visited the trial center at Months 1, 3, and 6, where researchers collected information about irregular heart rhythm events from their pacemaker.

Participants who received **ACEI** waited for 36 hours before moving to Part 2 of the trial. This was done to make sure that ACEI is completely removed from the participants' body before they took their next treatment.

Part 2 (Next 6 months)

- Starting from Month 7, participants took **LCZ696/ARNI** for 6 months.
- Participants visited the trial centers at Months 7, 9, and 12 for collection of information about irregular heart rhythm events from their pacemaker.
- By the end of Part 2, 140 out of 201 participants had received at least one dose of **LCZ696/ARNI**.

After treatment — 1 month

Participants received a follow-up call about 1 month after their last dose of treatment to assess their overall health.

What was the main result of this trial?

How many participants had irregular heart rhythm events during 6 months of LCZ696/ARNI treatment compared to 6 months of ACEI/ARB treatment?

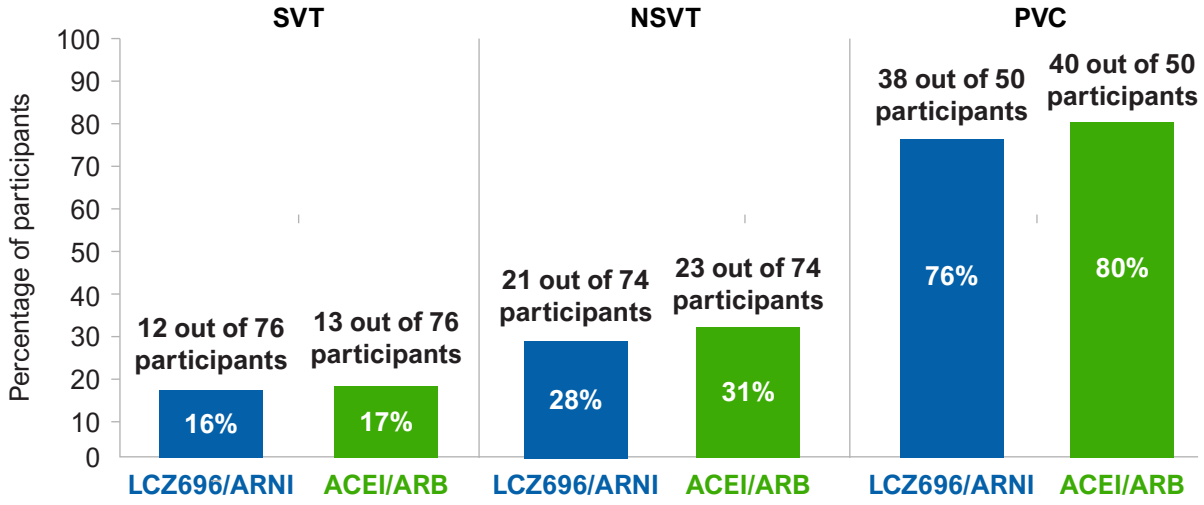
Overall, the number of participants who had irregular heart rhythm events was similar during the treatment with **LCZ696/ARNI** compared to the treatment with **ACEI/ARB**.

To answer this question, the researchers recorded irregular heart rhythm with a Holter heart monitoring device and pacemaker. They also analyzed other heart events that required the pacemaker to deliver electric shock generated to control irregular heartbeats.

They then counted and compared the number of participants with irregular heart rhythm events during their 6 months of treatment with **LCZ696/ARNI** and their 6 months of treatment with **ACEI/ARB**.

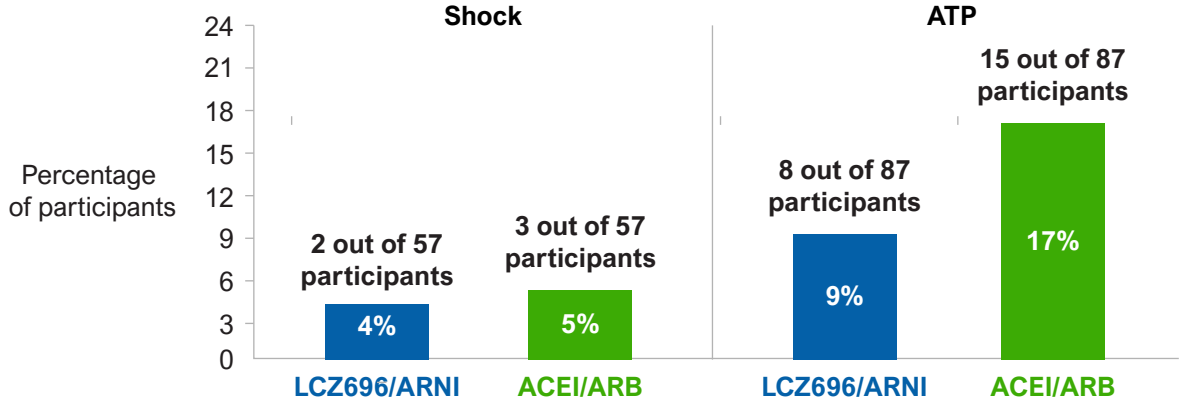
The trial doctors recorded the data for each event that happened in any of the participants. Not all the 140 participants who had received treatment with **LCZ696/ARNI** and 201 participants who had treatment with **ACEI/ARB** experienced all the irregular heart rhythm events.

Number (%) of participants with events of irregular heart rhythm



SVT: abnormal fast heartbeat that lasts 30 seconds or more; **NSVT:** abnormal fast heartbeat that lasts less than 30 seconds; **PVC:** extra heartbeat that disturbs the normal rhythm of the heart.

Number (%) of participants with at least one event of shock from the pacemaker



Shock: generated by pacemaker to control irregular heartbeats; **ATP:** continuous short series of low electrical shocks to the heart generated by pacemaker to control irregular heart rhythms.

What adverse events did the participants have?

Trial doctors keep track of all **adverse events** that happen in trials, even if they think the adverse events are not related to the trial treatments.

Many trials are needed to know if a drug or treatment causes an adverse event.

This section is a summary of the adverse events that happened from the start of the trial treatments up to 1 month after receiving the last dose of the trial treatment.

An **adverse event** is:

- Any **sign or symptom** that the participants have during a trial
- Considered **serious** when it is life-threatening, causes lasting problems, the participant needs hospital care, or results in death

Adverse events **may** or **may not** be caused by treatments in the trial.

65 out of 140 (46%) participants who took **LCZ696/ARNI** and 113 out of 201 (56%) participants who took **ACEI/ARB** had adverse events.

- 19 out of 140 (14%) participants who took **LCZ696/ARNI** and 38 out of 201 (19%) participants who took **ACEI/ARB** had adverse events that were considered serious.
- 3 participants in **ACEI/ARB** group died.
- No participant who took **LCZ696/ARNI** and 2 participants who took **ACEI/ARB** left the trial due to an adverse event.

The researchers concluded there were no new safety concerns for **LCZ696/ARNI** in this trial.

How many participants had adverse events?

Participants who:	LCZ696/ARNI 140 participants	ACEI/ARB 201 participants
Had at least 1 serious adverse event	19 of 140	38 of 201
Had at least 1 other adverse event	58 of 140	99 of 201
Left the trial due to an adverse event	0 of 140	2 of 201
Died during the trial	0 of 140	3 of 201

What serious adverse events did the participants have?

19 participants in **LCZ696/ARNI** group and 38 participants in **ACEI/ARB** group had serious adverse events. 3 participants died in the **ACEI/ARB** group.

The table below shows the most common serious adverse events that happened in **2 or more** participants in any treatment group.

	LCZ696/ARNI 140 participants	ACEI/ARB 201 participants
Heart failure Cardiac failure	4 of 140 3%	15 of 201 7%
Worsening of heart failure Cardiac failure chronic	2 of 140 1%	4 of 201 2%
Irregular heartbeat Atrial fibrillation	2 of 140 1%	0 of 201 0%
Fast heartbeat Ventricular tachycardia	2 of 140 1%	0 of 201 0%
Lung infection Pneumonia	1 of 140 less than 1%	4 of 201 2%
Pacemaker not working Lead dislodgement	0 of 140 0%	2 of 201 1%

What other adverse events did the participants have?

58 participants in **LCZ696/ARNI** group and 99 participants in **ACEI/ARB** group had other adverse events.

The table below shows the other adverse events that happened in **5 or more** participants in any treatment group.

	LCZ696/ARNI 140 participants	ACEI/ARB 201 participants
High levels of fat particles in the blood Hyperlipidaemia	**8 of 140** 6%	**4 of 201** 2%
Low blood pressure Hypotension	**7 of 140** 5%	**15 of 201** 7%
Chest discomfort	**4 of 140** 3%	**5 of 201** 2%
Common cold Upper respiratory tract infection	**3 of 140** 2%	**8 of 201** 4%
High levels of uric acid in the blood Hyperuricaemia	**3 of 140** 2%	**5 of 201** 2%
Feeling dizzy Dizziness	**2 of 140** 1%	**11 of 201** 5%
Cough	**1 of 140** less than 1%	**11 of 201** 5%

What was learned from this trial?

Researchers learned about the effects of **LCZ696/ARNI** on irregular heart rhythm in Chinese participants with HFrEF who have a pacemaker in their bodies to regulate their heartbeat.

- Researchers found that participants had similar irregular heart rhythm events when treated with **LCZ696/ARNI** or **ACEI/ARB**.
- Researchers found that the participants with HFrEF were able to tolerate the adverse effects of **LCZ696/ARNI**.

At the time this report was created, no future trials with **LCZ696/ARNI** were planned.

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**

Follow these steps to find the scientific summary:

Go to **www.novctrd.com** → Click **Clinical Trial Results** → Agree to the terms ☑ **I agree** → Search for **CLCZ696BCN04**

For more information about this trial, go to the website below:

- **clinicaltrials.gov** – search using the number **NCT04491136**

Other trials may appear on the public website above. When there, search for **LCZ696**, **ARNI** or Sacubitril/Valsartan.

Full clinical trial title: A multicenter, interventional, open-label and single-arm study to investigate the effect of ARNI on ventricular arrhythmia in HFrEF patients with ICD or CRT-D

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