NOVARTIS

# Clinical Trial Results Summary

## A clinical trial to learn more about the long-term safety of LCZ696 in children with heart failure

## Thank you!

Thank you to the children and families who took part in the clinical trial for heart failure (HF). Every participant helped the researchers learn more about the trial drug **LCZ696**, 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:** CLCZ696B2319E1

**Drug studied:** **LCZ696**, also known as sacubitril/valsartan

**Sponsor:** Novartis

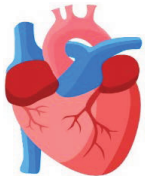
If you were a participant and have any questions about the results, please talk to the doctor or staff at the trial site.

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 more about the long-term safety of **LCZ696** in children with **heart failure (HF)** who completed the **core trial, CLCZ696B2319**.

The **core trial** compared the effects and safety of **LCZ696** with enalapril, an available medicine for **HF** in children. This trial is an extension of the core trial. Children could take part in the extension trial if they have successfully completed the **core trial** and received **LCZ696** in the **core trial.**



**Heart failure (HF)** is a long-term condition where the heart becomes too weak to pump enough blood throughout the body. This reduces the oxygen supply needed for normal function, causing symptoms like shortness of breath, weakness, fatigue, and swollen ankles and legs.

**LCZ696** contains 2 medicines, **sacubitril** and **valsartan**. It is approved in many countries for the treatment of **HF** in adults and children. **LCZ696** works by relaxing the blood vessels which helps reduce the workload on the heart. This improves the heart's capacity to pump blood to the body.

**Trial drug**
**LCZ696**, also called sacubitril/valsartan

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

**The trial's purpose was to answer this main question:**

- How many children had adverse events during this trial?
  - ↳ An **adverse event** is any sign or symptom that the participants had during a trial. Adverse events may or may not be caused by treatments in the trial.

# How long was this trial?

The trial began in May 2019 and ended in December 2023. An individual child could be in this trial for about 4 years and 5 months.

The researchers completed this trial as planned. When the trial ended, the researchers collected information from participants and created a report of the trial results. This summary is based on that report.

# Who was in this trial?

215 children with **heart failure (HF)** received treatment in this trial. Their average age was 9 years.

The number of children by age group, gender, and race are shown below.

**Age group**

| | |
|---|---|
| 130 6 years and above | 85 1 to less than 6 years |

**Gender**

| | |
|---|---|
| 106 Boys | 109 Girls |

**Race**

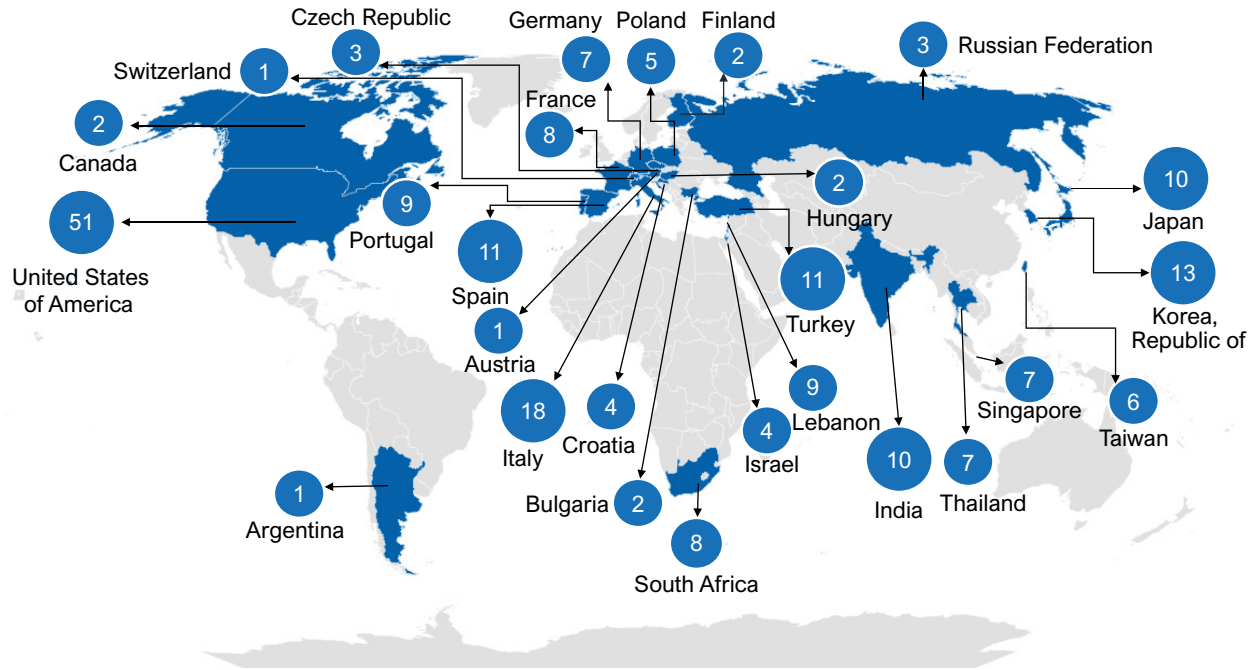
| | | |
|---|---|---|
| 2 American Indian or Alaska Native | 47 Asian | 29 Black or African American |
| 1 Native Hawaiian or Pacific islander | 119 White | 4 More than 1 race |
| 13 Unknown | | |

Children could take part in this trial if they:

- have successfully completed the **core trial** and received **LCZ696** in the **core trial**, or
- had to stop the **core trial** early due to **urgent safety concerns**

The urgent safety concerns were related to the expiry date of enalapril. Later, a thorough investigation revealed that there was no risk or harm to the participants.

215 children from 27 countries received treatment. The map below shows the number of children who took part in each country.




# What treatment did the children receive?

The treatment in this trial was:

**LCZ696**, also known as sacubitril/valsartan, given orally twice daily. It came in 3 forms: tablets, capsules containing granules, and liquid suspension. Children took **LCZ696** in any form based on their age.

Children started with a lower dose of **LCZ696**, which was gradually increased until they reached the target dose of 3.1 milligram (mg) for every kilogram of children's body weight, twice daily.

After the **core trial,** some children switched to a type of blood pressure lowering medicine called angiotensin-converting enzyme inhibitor **(ACEI)**. A gap of at least 36 hours was kept between the last dose on the **core trial** or of the **ACEI** and the first dose of **LCZ696** in this trial.

Children started taking **LCZ696** in the **extension trial** within 30 days after the **core trial.**

In this trial, the parents/guardians, researchers, and trial staff knew what treatment each child received.

# What happened during this trial?

## Before treatment — 1 day

Trial doctors checked the children's health to ensure they could be in this trial.

## During treatment — Up to 4.5 years

215 children received treatment in this trial. Children were divided into 2 groups based on their age.

| Group 1<br>Children 6 years of age and above | Group 2<br>Children between 1 to less than 6 years of age |
|---|---|
| 130 participants | 85 participants |

- For each child, the trial doctor started **LCZ696** at a low dose and gradually increased the dose of **LCZ696** to the target level over a few weeks, depending on how well the children tolerated the treatment.
- Children could receive **LCZ696** for at least 1 year, until it became available in the market, or until December 2023, whichever came first.
- Safety checks were conducted every 3 months, with additional visits every 2 weeks during dose adjustments.

## After treatment

Children returned to the trial site every 3 months for health check-ups until the end of the trial.

# What were the main results of this trial?

## How many children had adverse events during this trial?

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 treatment up to 4.5 years.

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.

189 out of 215 children had adverse events. 84 children had adverse events that were considered serious. 17 participants left the trial due to an adverse event. 11 children died during the trial. The researchers concluded there were no new safety concerns with the use of **LCZ696** in this trial.

| **Children who:** | **Group 1 (6 years and above)** 130 participants | **Group 2 (1 to less than 6 years)** 85 participants |
|---|---|---|
| Had at least 1 serious adverse event | **59 of 130** 45% | **25 of 85** 29% |
| Had at least 1 other adverse event | **111 of 130** 85% | **78 of 85** 92% |
| Left the trial due to an adverse event | **16 of 130** 12% | **1 of 85** 1% |
| Died | **7 of 130** 5% | **4 of 85** 5% |

## What serious adverse events did the children have?

84 children had serious adverse events. The following most common serious adverse events were reported by **3% or more** children in either group:

| | Group 1 (6 years and above) 130 participants | Group 2 (1 to less than 6 years) 85 participants |
|---|---|---|
| **Chest pain** | **5 of 130** 4% | **0** |
| **COVID-19** | **4 of 130** 3% | **4 of 85** 5% |
| **Enlargement and weakening of heart muscles** Dilated cardiomyopathy | **5 of 130** 4% | **0** |
| **Fever** Pyrexia | **3 of 130** 2% | **3 of 85** 4% |
| **Heart failure** Cardiac failure | **15 of 130** 12% | **3 of 85** 4% |
| **Inflammation of the stomach** Gastroenteritis | **4 of 130** 3% | **2 of 85** 2% |
| **Long term heart failure** Cardiac failure chronic | **4 of 130** 3% | **2 of 85** 2% |
| **Lung Infection** Pneumonia | **5 of 130** 4% | **4 of 85** 5% |

## What other adverse events did the children have?

189 children had other adverse events. The table below shows the other adverse events that happened in **10% or more** children in either group.

| | Group 1 (6 years and above) 130 participants | Group 2 (1 to less than 6 years) 85 participants |
|---|---|---|
| **Cough** | **20 of 130** 15% | **19 of 85** 22% |
| **COVID-19** | **23 of 130** 18% | **24 of 85** 28% |
| **Diarrhea** | **9 of 130** 7% | **9 of 85** 11% |
| **Dizziness** | **14 of 130** 11% | **0** |
| **Fever** Pyrexia | **15 of 130** 12% | **22 of 85** 26% |
| **Headache** | **15 of 130** 12% | **3 of 85** 4% |
| **Infection of the nose and throat** Upper respiratory tract infection | **8 of 130** 6% | **22 of 85** 26% |
| **Inflammation of the nose and throat** Nasopharyngitis | **12 of 130** 9% | **14 of 85** 16% |
| **Low blood pressure** Hypotension | **18 of 130** 14% | **3 of 85** 4% |
| **Tested positive for COVID-19 infection** SARS-CoV-2 test positive | **13 of 130** 10% | **1 of 85** 1% |
| **Vomiting** | **15 of 130** 12% | **12 of 85** 14% |

# What was learned from this trial?

Researchers learned more about the safety of **LCZ696** in children with **heart failure (HF)** who completed the **core trial**.

Researchers found that:

- long-term use of **LCZ696** did not affect the growth, bone development, or bone health of children with **HF**
- there were no new safety concerns with the use of **LCZ696** in this trial

When this summary was written, there were no plans for future trials with **LCZ696** in children with **HF**.

# 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 of this **extension trial**:


Follow these steps to find the scientific summary of the **core trial**:


For more information about the **extension trial**, go to any of these websites:

- www.clinicaltrials.gov - search using the number **NCT03785405**
- clinicaltrialsregister.eu/ctr-search/search - search using the number **2018-004154-25**

If more trials are planned, they will appear on the public websites above. When there, search for **LCZ696**, or sacubitril/valsartan.

**Full clinical trial title:** A multicenter study to evaluate long-term safety and tolerability of open label sacubitril/valsartan in pediatric patients with heart failure due to systemic left ventricle systolic dysfunction who have completed study CLCZ696B2319

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