

Clinical Trial Results Summary

A clinical trial to learn more about the effects of different doses of **XXB750 in people with heart failure**

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 **XXB750**.

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: CXXB750A12201

Novartis drug studied: **XXB750**

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 results.

What was the main purpose of this trial?

The purpose of this trial was to learn about the effects of different doses of **XXB750** in people with **heart failure**. To find this out, researchers compared the effects of different doses of **XXB750** to **placebo** and **sacubitril/valsartan**.



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



XXB750 is a drug designed to directly activate a protein (receptor) in the body in order to help relax blood vessels and decrease sodium and fluid in the body to reduce the stress on the heart.



A **placebo** looks like a trial drug but does not have any drug in it. Using a placebo helps researchers better understand the effect of a trial drug.



Sacubitril/valsartan is approved in many countries for the treatment of **HF**. It 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
sacubitril/valsartan
Pronounced as
SAH-kyoo-BEE-tril/
val-SAR-tan

During this trial, participants continued to take their **standard medicines** for **HF**, except the participants in the **sacubitril/valsartan** group. In these participants, one of the **standard medicines** for **HF** was switched to **sacubitril/valsartan**.



The trial's purpose was to answer these main questions:

- Do participants who receive different dose levels of **XXB750** experience a lowering of their **N-terminal pro-B-type natriuretic peptide (NT-proBNP)** levels, when compared to **placebo** and **sacubitril/valsartan**?
- What medical problems, also called adverse events, happen during this trial?
 - ↳ An **adverse event** is any sign or symptom that participants have during a trial. Adverse events **may** or **may not** be caused by treatments in the trial.

NT-proBNP is made by heart muscles when the heart has to work hard. People with **HF** have high levels of **NT-proBNP** in the blood because their heart is weak and needs to work hard all the time. Measuring the **NT-proBNP** levels in the blood can help doctors identify **HF**.

How long was this trial?



The trial began in December 2023. Individual participants were planned to be in this trial for about 6 months.

Due to safety concerns and an increased number of **HF** worsening events in the participants receiving **XXB750**, treatment with **XXB750** was stopped in August 2024 and the trial ended in November 2024.

Based on some of the **standard medicines** for **HF** they were already taking, participants were originally planned to be divided into a total of 5 groups.

If a participant had been taking **sacubitril/valsartan** as one of their **standard medicines** for **HF** before this trial, they were randomly assigned to:

- **XXB750** at either a **low dose (60 milligrams (mg))**, **medium dose (120 mg)**, or **high dose (240 mg)**: as the trial ended early, none of the participants received the **high dose**, or
- **placebo**

If a participant had been taking an **angiotensin converting enzyme inhibitor (ACEI)** or an **angiotensin receptor blocker (ARB)** as one of their **standard medicines** for **HF** before this trial, they were randomly assigned to:

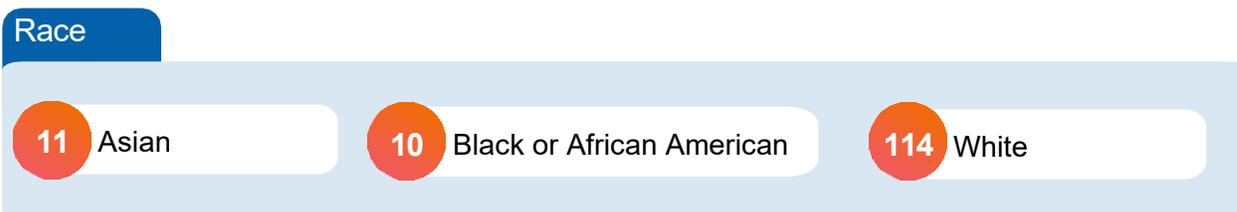
- **XXB750** at either a **low dose (60 mg)**, **medium dose (120 mg)**, or **high dose (240 mg)**: as the trial ended early, none of the participants received the **high dose**, or
- **placebo**, or
- **sacubitril/valsartan**

Who was in this trial?



136 participants with **HF** were enrolled in this trial. Of these, 1 participant was mistakenly enrolled even though they did not meet the trial-specific requirements and did not receive any trial treatment. Therefore, 135 participants – 94 men and 41 women were included in the trial. Participants' ages ranged from 38 to 91 years. The average age was 70 years.

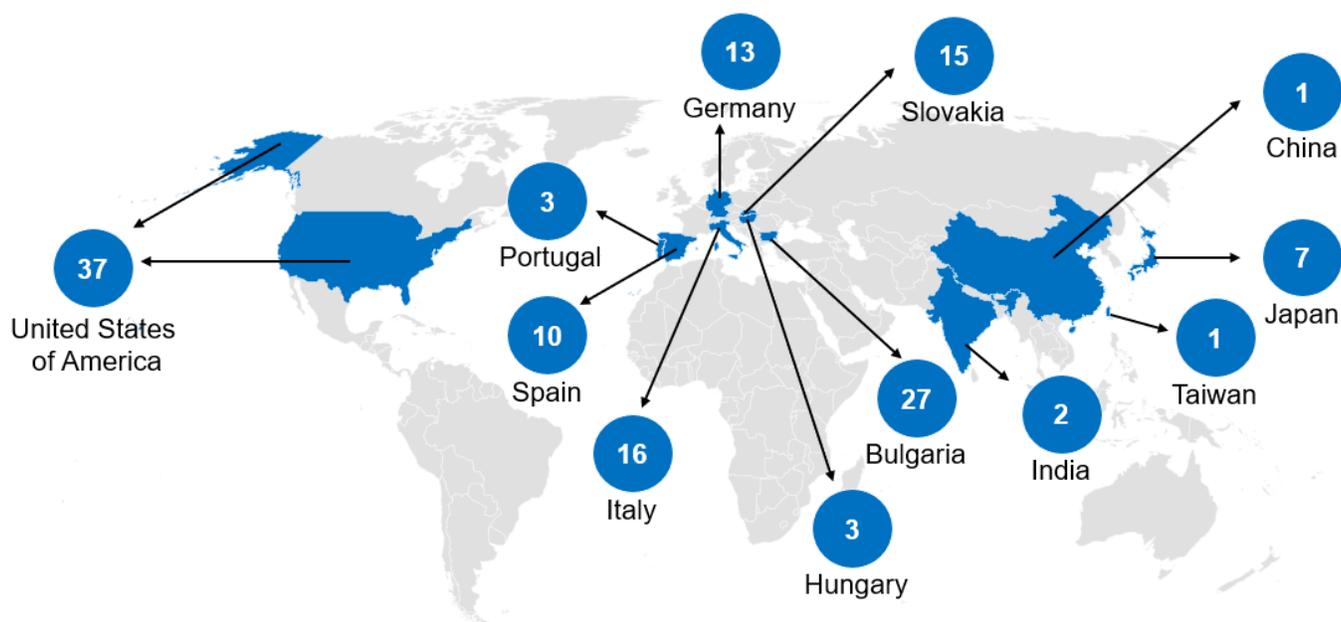
The number of participants by race is shown below.



The participants could take part in this trial if they:

- were at least 18 years of age
- had a left ventricular ejection fraction (i.e., proportion of blood pushed out of the heart's left ventricle) of less than 50%; up to 6 months before joining this trial
- had higher than normal levels of **NT-proBNP** in their blood

135 participants from 12 countries took part in this trial. The map below shows the number of participants who took part in each country.



What treatments did the participants receive?

The treatments in this trial were:



XXB750, given as an injection under the skin once every 4 weeks. While this trial was originally planned to study 3 different doses of **XXB750**, only 2 doses were tested.

Each participant received either:

- **Low dose: 60 mg**
- **Medium dose: 60 mg** at the first visit, followed by **120 mg** at the following visits

As the trial ended early, participants did not receive the planned **high dose** of **XXB750**

- **High dose: 240 mg**



Placebo was given as an injection under the skin once every 4 weeks.



Sacubitril/valsartan was taken as tablets by mouth, twice a day. The participants started at a **49/51 mg** dose or a **24/26 mg** dose of **sacubitril/valsartan** as per the trial doctor's choice. Over the first 4 weeks of the trial, the dose was increased to **97/103 mg** twice a day. The doses could also be reduced based on the recommendation of the trial doctor.

In addition to receiving **XXB750** or **placebo**, participants continued all their **standard medicines** for **HF**. For participants in the **sacubitril/valsartan** group, treatment with an **angiotensin converting enzyme inhibitor (ACEI)** or an **angiotensin receptor blocker (ARB)** was discontinued before starting **sacubitril/valsartan**

In the **XXB750** or **placebo** treatment groups, participants, researchers, and trial staff did not know what treatment the participants were receiving. In the **sacubitril/valsartan** group, the researchers, participants, and the trial staff knew what treatment the participants were receiving.

What happened during this trial?

Before treatment

Approximately 1 week



The trial staff checked to make sure the participants could be in this trial.

During treatment

Up to 4 months

Participants in this trial were randomly divided into 4 groups using a computer program based on their **standard medicines** for HF.

- Participants who took **sacubitril/valsartan** before joining the trial were assigned to receive different doses of either: **XXB750** or a **placebo** by injection every 4 weeks. Participants receiving **XXB750** or a **placebo** continued their **standard HF** medicines.
- Participants who took an **ACEI** or **ARB** before joining this trial received different doses of either: **XXB750** or a **placebo** by injection every 4 weeks, or **sacubitril/valsartan** orally. Participants receiving **XXB750** or a **placebo** continued their **standard HF** medicines. Participants who received **sacubitril/valsartan** discontinued treatment with an **ACEI** or **ARB** while continuing their other **standard medicines** for HF.



60mg of **XXB750**

26 participants



60mg of **XXB750** followed by **120 mg** of **XXB750**

55 participants



Placebo

29 participants



Sacubitril/valsartan

25 participants

After treatment

Up to 12 weeks



Trial staff checked participants' general health and for any medical problems for 12 weeks after the participant's last dose of **XXB750** or **placebo**.

What were the main results of this trial?

Do participants who receive different dose levels of **XXB750** experience a lowering of their **NT-proBNP** levels, when compared to **placebo** and **sacubitril/valsartan**?

To answer this question, researchers measured the levels of **NT-proBNP** in the participants' blood after 16 weeks of treatment.



Due to the trial ending earlier than planned there weren't enough participants for the researchers to analyze the results as planned. This means they couldn't draw a definite conclusion from the trial.

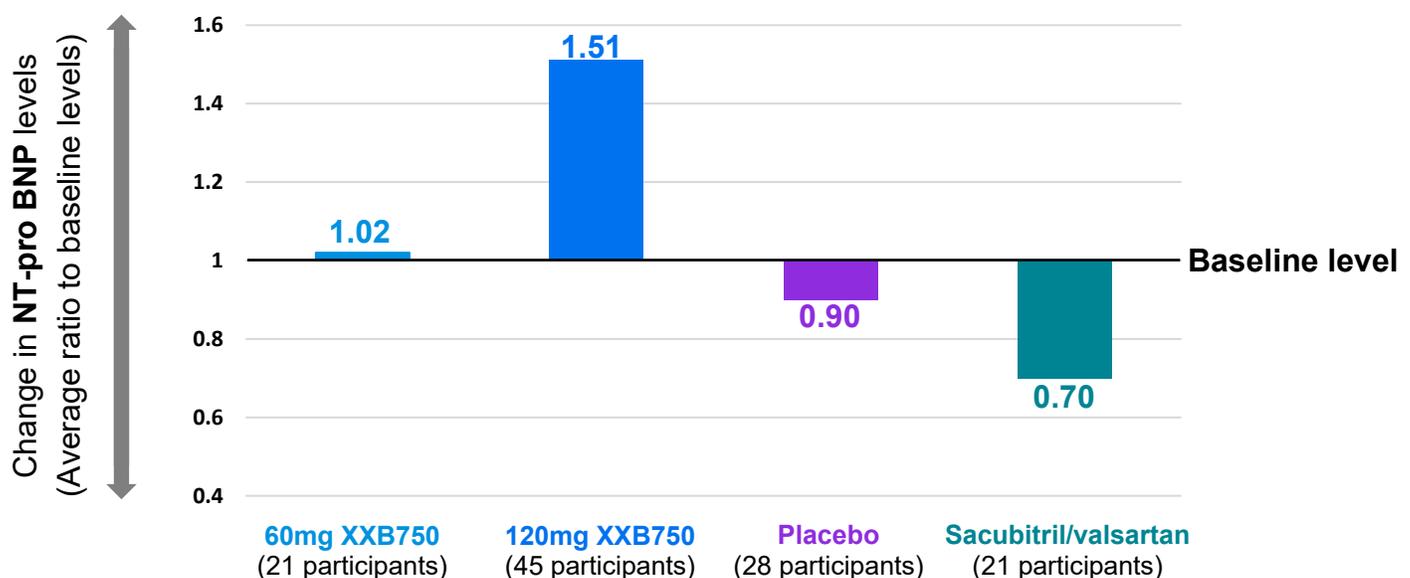
NT-proBNP is made by heart muscles when the heart has to work hard. People with **HF** have high levels of **NT-proBNP** in the blood because their heart is weak and needs to work hard all the time. Measuring the **NT-proBNP** levels in the blood can help doctors identify **HF**.

A reduction in **NT-proBNP** level meant improvement in the participants **HF** symptoms. In this trial, researchers expected to see a reduction in **NT-proBNP** with **XXB750** and **sacubitril/valsartan** compared to **placebo**.

As the trial ended early, some participants who entered the trial did not complete all the trial assessments. Thus, the results were available for 115 participants.

After 16 weeks of treatment, different doses of **XXB750** did not show a reduction in **NT-proBNP** levels in the participants' blood compared with **placebo** and **sacubitril/valsartan**.

Average change in participants **NT-proBNP** levels after 16 weeks of treatment



What medical problems, also called adverse events, happened during this trial?

Trial doctors keep track of all medical problems, also called **adverse events**, that happen in trials. They track adverse events 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 until 3 months after the last treatment.

One participant who entered the trial did not receive the assigned treatment. Therefore, the safety results were available for 134 participants.

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.



77 of 134 participants had adverse events. 30 participants had adverse events that were considered serious. 5 participants died. 2 participants left the trial due to an adverse event.

The trial was stopped early due to safety concerns and an increased number of **HF** worsening events in the participants.

What serious adverse events did the participants have?

30 participants had serious adverse events. The table below shows the most common serious adverse events.

	XXB750 60mg 26 participants	XXB750 120 mg 54 participants	Placebo 29 participants	Sacubitril/ valsartan 25 participants
Heart failure Cardiac failure	1 of 26 4%	5 of 54 9%	0	1 of 25 4%
Sudden heart failure Cardiac failure acute	1 of 26 4%	1 of 54 2%	0	0
Heart failure, which makes you short of breath Cardiac failure congestive	0	2 of 54 4%	0	0
Serious kidney problems Acute kidney injury	3 of 26 12%	1 of 54 2%	0	0
Lung infection Pneumonia	2 of 26 8%	1 of 54 2%	0	0
High volume of fluid in the body Hypervolemia	1 of 26 4%	1 of 54 2%	0	0
Black stools Melena	0	1 of 54 2%	1 of 29 3%	0

What other (not including serious) adverse events did the participants have?

The table below shows the most common other adverse events. Additional adverse events happened in fewer participants.

	XXB75060mg 26 participants	XXB750 120 mg 54 participants	Placebo 29 participants	Sacubitril/ valsartan 25 participants
Heart failure Cardiac failure	4 of 26 15%	7 of 54 13%	0	0
Low blood pressure Hypotension	4 of 26 15%	7 of 54 13%	2 of 29 7%	6 of 25 24%
Fast uneven heartbeat Atrial fibrillation	1 of 26 4%	2 of 54 4%	2 of 29 7%	1 of 25 4%
Increased levels of urea in the blood Blood urea increased	2 of 26 8%	0	1 of 29 3%	2 of 25 8%
Increased levels of creatinine in the blood Blood creatinine increased	1 of 26 4%	0	1 of 29 3%	3 of 25 12%
Infection in the urinary system Urinary tract infection	3 of 26 12%	2 of 54 4%	0	2 of 25 8%
Difficulty breathing Dyspnea	4 of 26 15%	4 of 54 7%	0	0
COVID-19 infection COVID-19	0	0	2 of 29 7%	0

What was learned from this trial?

Researchers learned about the effects of **XXB750** in people with **HF**. Due to the trial ending earlier than planned there weren't enough participants for the researchers to analyze the results as planned. This means they couldn't draw a definite conclusion from the trial.



However, after 16 weeks of treatment, different doses of **XXB750** did not show a reduction in **NT-proBNP** levels in the participants' blood, as compared with **placebo** and **sacubitril/valsartan**.

The trial was terminated early due to safety concerns and an increased number of **HF** worsening events in the participants receiving **XXB750**.

When this summary was written, the sponsor had no plans for future trials of **XXB750** in people 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:



For more information about this trial, go to any of these websites:

- clinicaltrials.gov – search using the number **NCT06142383**
- euclinicaltrials.eu – search using the number **2023-504678-39-00**

Other trials of **XXB750** may appear on the public websites above. When there, search for **XXB750**.

Full clinical trial title: A multi-center, randomized, placebo- and active-controlled, parallel-group, 24-week proof of concept and dose-finding study to evaluate efficacy, safety, and tolerability of XXB750 in patients with heart failure



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