NOVARTIS

Clinical Trial Results Summary

A clinical trial to learn more about the effects of LJN452, LIK066, and their combination in adult people with nonalcoholic steatohepatitis and liver fibrosis compared with placebo

Thank you!

Thank you to the participants who took part in the clinical trial for nonalcoholic steatohepatitis and liver fibrosis. Every participant helped the researchers learn more about the trial drugs **LJN452**, also called tropifexor and **LIK066**, also called licogliflozin.

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: CLJN452D12201C

Drug studied: LJN452 (tropifexor), LIK066 (licogliflozin)

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 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 find the effects of **LJN452**, **LIK066**, and the combination of both these drugs in people with nonalcoholic steatohepatitis and liver fibrosis.
To find this out, researchers wanted to compare the effects of **LJN452**, **LIK066**, and their combination with placebo.

Nonalcoholic steatohepatitis (NASH) is also known as **'fatty liver disease'**. In fatty liver disease, fat builds up in the liver, which leads to swelling and damage to the liver. Over time, this may lead to liver fibrosis and cause permanent damage to the liver.

Liver fibrosis, in liver fibrosis, the liver tissue becomes scarred, which can prevent the liver from working as well as it should.

LJN452, also known as tropifexor, works by increasing the activity of specific proteins in the liver, intestine, and kidneys. These proteins help the liver to work as well as it should.

LIK066, also known as licogliflozin, works by lowering the body's ability to absorb glucose and by blocking the kidneys from reabsorbing glucose.

LJN452 and **LIK066** are being developed as possible treatments for people with NASH and liver fibrosis.

The trial purpose was to answer these main questions:

- After 48 weeks of treatment, did **LJN452** or **LIK066** alone, or in combination, improve participants' liver fibrosis by at least **one stage*** without worsening of their NASH?
- After 48 weeks of treatment, did **LJN452** or **LIK066** alone, or in combination, show a resolution of participants' NASH without worsening of their liver fibrosis?
- What adverse events did the participants have during this trial?
  - ↳ An **adverse event** is any sign or symptom that participants have during a trial.

*Liver fibrosis has 5 stages. The fibrosis stages range from F0 (no fibrosis) to F4 (irreversible loss of liver function).

In this trial, participants had stage F2 (mild to moderate) or F3 (severe) liver fibrosis at the start of the trial.

How long was this trial?

The trial began in December 2019 and ended in October 2022.

It was planned for 380 participants to be in this trial for about a year after starting the trial treatment. In July 2022, the researchers made the decision to stop this trial early after 233 participants were enrolled.

The sponsor made a business decision to stop the development of the trial drugs. The decision to stop the trial early was not because of safety concerns.

Who was in this trial?

233 participants with NASH and liver fibrosis received treatment in this trial. Participants' ages ranged from 22 to 79 years. Their average age was 55 years.

The number of participants by gender and race are shown below.

Gender

- 104 Men
- 129 Women

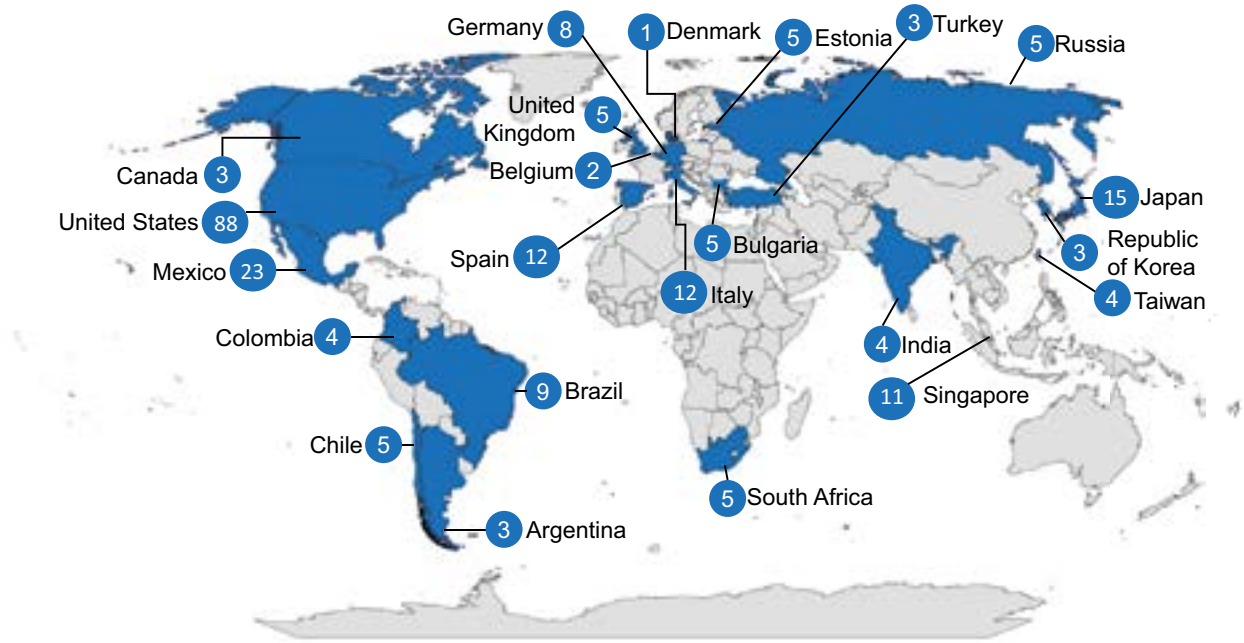
Race

- 174 White
- 41 Asian
- 8 American Indian or Alaska Native
- 7 Black or African American
- 2 Not reported
- 1 Native Hawaiian or Other Pacific Islander

The participants could take part in this trial if they:

- had NASH with liver fibrosis
- did not have diabetes, low platelet levels, or other liver diseases

233 participants from 23 countries received treatment. 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:

LJN452, 140 micrograms (µg) taken by mouth as capsules.

LIK066, 30 milligrams (mg) taken by mouth as tablets.

A **placebo** looks like the trial drug but does not have any drug in it. This placebo could look like **LJN452** capsules or **LIK066** tablets. Using a placebo ensured that the trial staff and the participants did not know if the participants were taking **LJN452** or **LIK066**.

None of the participants, trial doctors, or trial staff knew what treatment the participants were receiving. Some trials are done this way because knowing what treatment the participants receive can affect the results of the trial. Doing a trial this way helps to make sure that the results are looked at with fairness across all treatments.

What happened during this trial?

Before treatment — Up to 10 weeks

Trial doctors checked the participants' health and health condition to ensure they could take part in this clinical trial.

During treatment — Up to 48 weeks

Researchers used a computer program to randomly place participants into 4 different treatment groups. This means that each person could end up in any of the treatment groups. Treatment was given once daily in the following combinations:

The number of participants listed below completed 48 weeks of treatment.

Group 1 (53 participants): participants took a 140 µg **LJN452** capsule and a **placebo** that looked like the **LIK066** tablet

Group 2 (55 participants): participants took a 30 mg **LIK066** tablet and a **placebo** that looked like the **LJN452** capsule

Group 3 (84 participants): participants took 140 µg **LJN452** as a capsule and 30 mg **LIK066** as a tablet

Group 4 (41 participants): participants took a **placebo** capsule that looked like the **LJN452** capsule and a **placebo** tablet that looked like the **LIK066** tablet

After treatment — 4 weeks

The participants returned to their trial site multiple times after treatment. During these visits, the researchers checked the participants' health.

What were the main results of this trial?

After 48 weeks of treatment, did LJN452 and LIK066 alone, or in combination, improve participants' liver fibrosis by at least one stage without worsening of their NASH?

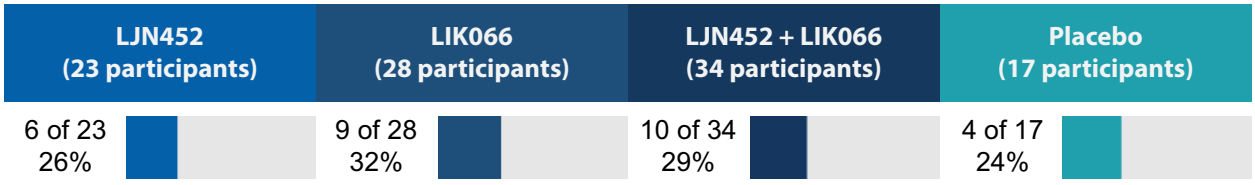
After 48 weeks of treatment, researchers found that there was no meaningful difference in the number of participants who had an improvement in their liver fibrosis without worsening of their NASH in each treatment group.

No conclusion could be confirmed as this trial was stopped early.

To answer this question, the trial doctors took liver tissue samples from the participants before and after the treatment. They did this to find out how much liver tissue was scarred. They then counted how many participants had a decrease in the extent of scarred liver tissue after 48 weeks of treatment.

The results were assessed for the participants who completed 48 weeks of treatment.

Number (percentage) of participants with improvement in their liver fibrosis



After 48 weeks of treatment, did LJN452 and LIK066 alone, or in combination, show a resolution of participants' NASH without worsening of their liver fibrosis?

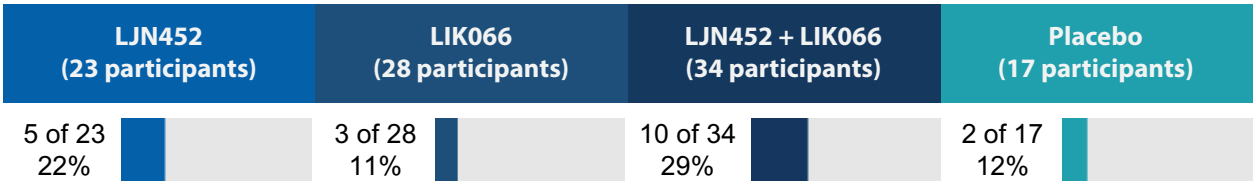
After 48 weeks of treatment, slightly more participants in the **LJN452** group and **LJN452** and **LIK066** combination group had a resolution of their NASH without worsening of their liver fibrosis compared with the **LIK066** groups and **placebo** group.

No conclusion could be confirmed as this trial was stopped early.

To answer this question, the trial doctors used the same liver tissue samples taken from the participants before and after the treatment. They did this to find out how much liver tissue was scarred. They then counted how many participants had resolution of NASH without worsening of their liver fibrosis after 48 weeks of treatment.

The results were assessed for the participants who completed the 48 weeks of treatment.

Number (percentage) of participants with a decrease in the severity of their NASH



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 trial treatment up to 4 weeks after the end of 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.

185 out of 233 participants had adverse events. 14 participants had adverse events that were considered serious. 31 participants stopped the trial treatment due to an adverse event. No participant died during the trial. The researchers concluded that there were no new safety concerns with the combination of **LJN452** and **LIK066** from this trial.

How many participants had adverse events?

Participants who:	LJN452 (53 participants)	LIK066 (55 participants)	LJN452 + LIK066 (84 participants)	Placebo (41 participants)
Had at least 1 adverse event	41 of 53 77%	46 of 55 84%	68 of 84 81%	30 of 41 73%
Had at least 1 serious adverse event	4 of 53 8%	3 of 55 6%	4 of 84 5%	3 of 41 7%
Stopped treatment due to an adverse event	7 of 53 13%	2 of 55 4%	21 of 84 25%	1 of 41 2%
Died during the trial	0	0	0	0

What serious adverse events did the participants have?

14 participants had serious adverse events. The following serious adverse events were experienced by 1 participant each in the respective treatment groups:

List of serious adverse events that occurred in each treatment group.

LJN452	LIK066	LJN452 + LIK066	Placebo
• **Bleeding in the stomach** (haemoperitoneum) • **Heart failure** (cardiac failure chronic) • **Inflammation of the gall bladder** (cholecystitis) • **Inflammation of the pancreas** (pancreatitis) • **Lung infection due to COVID-19** (COVID-19 pneumonia) • **Prostate cancer**	• **Cancer of the ovaries** (ovarian cancer) • **Fever after a medical procedure** (post-procedural fever) • **Inflammation of the digestive tract** (gastroenteritis) • **Liver infection** (hepatitis E)	• **Bleeding inside the biliary tract** (haemobilia) • **Low number of red blood cells in the blood** (anemia) • **Pain going down the leg** (sciatica) • **Pain in the chest that is not related to the heart** (non-cardiac chest pain)	• **Difficulty in breathing due to disease of the lungs** (asthma) • **Irregular heartbeat** (atrial fibrillation) • **Kidney stones** (calculus urinary) • **Stomach pain** (abdominal pain)

What other adverse events did the participants have?

185 participants had other adverse events. The table below shows the other adverse events that happened in **10% or more** participants in any treatment group during the trial.

	LJN452 (53 participants)	LIK066 (55 participants)	LJN452 + LIK066 (84 participants)	Placebo (41 participants)
Itching (Pruritus)	20 of 53 38%	9 of 55 16%	22 of 84 26%	4 of 41 10%
Diarrhea	7 of 53 13%	21 of 55 38%	21 of 84 25%	6 of 41 15%
COVID-19 infection	1 of 53 2%	10 of 55 18%	9 of 84 11%	9 of 41 22%
Headache	2 of 53 4%	1 of 55 2%	3 of 84 4%	6 of 41 15%
Vomiting	7 of 53 13%	2 of 55 4%	3 of 84 4%	2 of 41 5%
Feeling sick (Nausea)	6 of 53 11%	4 of 55 7%	7 of 84 8%	2 of 41 5%
Infection in the urinary system (Urinary tract infection)	3 of 53 6%	6 of 55 11%	4 of 84 5%	2 of 41 5%

What was learned from this trial?

Researchers learned about the effects of **LJN452**, **LIK066**, and their combination in people with NASH and liver fibrosis.

The researchers found that after 48 weeks of treatment:

- there was no meaningful difference in the number of participants who had an improvement in their liver fibrosis without worsening of their NASH in each treatment group
- slightly more participants in the **LJN452** group and **LJN452** and **LIK066** combination group had a resolution of their NASH without worsening of their liver fibrosis compared with the **LIK066** group and placebo group

However, no conclusion can be confirmed as this trial was stopped early.

Researchers did not find any new safety concerns with **LJN452**, **LIK066**, and the combination of both these drugs.

When this summary was written, there were no plans for future trials with **LJN452**, **LIK066**, and the combination of both these drugs in people with NASH and liver fibrosis.

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 the following websites:

- **www.clinicaltrials.gov** - search using the number **NCT04065841**
- **clinicaltrialsregister.eu/ctr-search/search** - search using the number **2019-002324-32**

If more trials are planned, they will appear on the public websites above.

When there, search for LJN452, tropifexor, LIK066, licogliflozin, NASH or liver fibrosis.

Full clinical trial title: A randomized, double-blind, parallel-group, multicenter study to assess efficacy, safety, and tolerability of oral tropifexor (LJN452) & licogliflozin (LIK066) combination therapy and each monotherapy, compared with placebo for treatment of adult participants with nonalcoholic steatohepatitis (NASH) and liver fibrosis (ELIVATE)

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