NOVARTIS

Clinical Trial Results Summary

A clinical trial to learn about the effects of LMI070 in people with Huntington's disease

Thank you!

Thank you to the participants who took part in the clinical trial for Huntington's disease. Every participant helped the researchers learn more about the trial drug **LMI070**, also called branaplam.

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: CLMI070C12203

Drug studied: LMI070, also called branaplam

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 find a safe and effective dose of **LMI070** for people with **Huntington's disease.**

Huntington's disease (HD) is a rare condition inherited from a parent through a genetic mutation (change) in the **Huntingtin (HTT) gene** which contains instructions for making **HTT protein**. The mutated **HTT** gene causes an abnormal HTT protein (**mHTT** protein) to form in the brain which can be detected in **cerebrospinal fluid (CSF*)**.

***CSF** is a clear, colorless fluid that surrounds the brain and spinal cord and protects these organs from an injury.

This mutated (**mHTT**) protein can cause the nerve cells to die slowly over time and eventually affect a person's nerve cell function, movement, ability to think, and mental health.

Researchers believe that lowering the levels of **mHTT** protein in the brain could slow down the progression of **HD**.

LMI070, also called branaplam, is an investigational trial drug being studied to lower the levels of **HTT** protein (both mutated and normal) which could slow the progression of **HD**.

In this trial, researchers wanted to compare different doses of **LMI070** to find which doses were safe and could lower **mHTT** protein levels in the **CSF** as compared to **placebo**.

Trial drug
LMI070 also called branaplam

Pronounced as

BRAN-uh-plam

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

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

- What was the change in the levels of **mHTT** protein in the cerebrospinal fluid (**CSF**) of the participants after 16 weeks of treatment with **LMI070** as compared to **placebo**?
- How many participants had adverse events during this trial?
  - An **adverse event** is any sign or symptom that participants have during a trial that **may** or **may not** be caused by the study treatments.

How long was this trial?

The trial began in December 2021 and ended in October 2023. It was planned initially for participants to be in this trial for a total duration of up to 2 and a half years.

Some participants who received **LMI070** showed signs and/or symptoms of **peripheral neuropathy**. Therefore, in December 2022, the sponsor stopped this trial early for safety concerns.

This trial was planned to have **2 treatment periods. Treatment Period 1** was planned to find a safe and effective dose of **LMI070** that could lower **mHTT** appropriately and be further studied in **Treatment Period 2**. However, the trial ended early before treatment in **Period 2** could be started.

Peripheral neuropathy happens when the nerves outside the brain and spinal cord (peripheral nerves) are damaged. This condition often causes weakness, numbness and pain, usually in the hands and feet.

Who was in this trial?

26 participants with **Huntington's disease (HD)** received treatment in this trial. Participants' ages ranged from 27 to 66 years. Their average age was about 50 years.

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

Gender

15 **Men**	11 **Women**

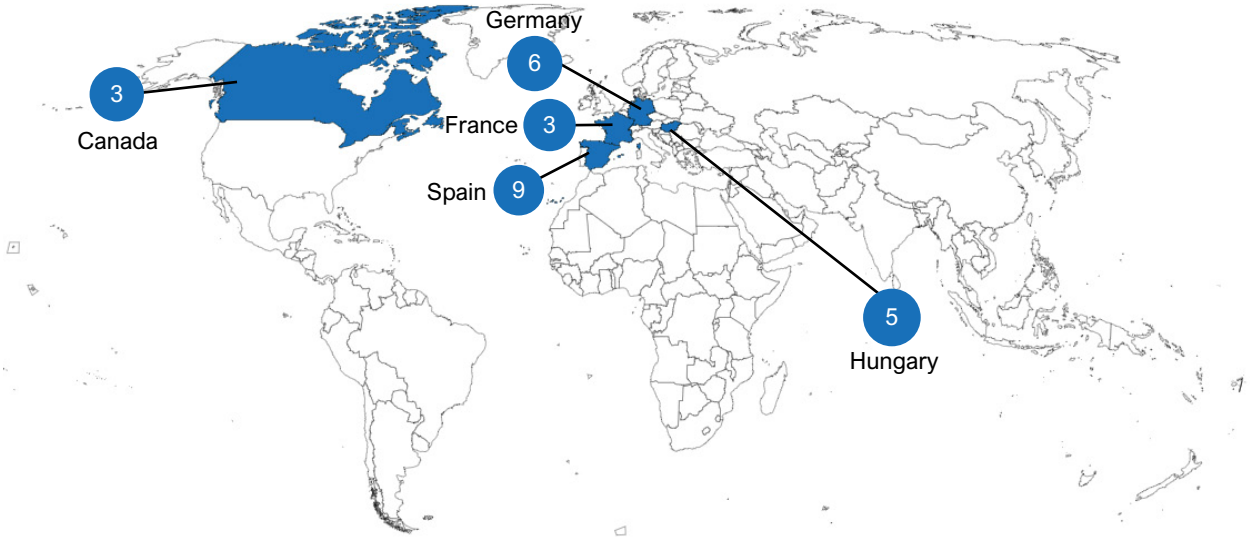
Race

23 **White**	3 **Unknown**

The participants could take part in this trial if they:

- were between 25 and 75 years of age
- had a confirmed **Huntington's disease (HD)** with mild or more noticeable symptoms
- had not received a huntingtin-lowering treatment as part of a clinical trial previously

26 participants from 5 countries received treatment. The map below shows the number of participants who took part in each country.



What treatments did the participants receive?

During **Treatment Period 1**, researchers planned to study 3 different increasing doses of **LMI070**. However, they only tested the lowest dose of **LMI070**.

The treatments that were given during **Treatment Period 1** were:

LMI070, also known as branaplam, 56 milligrams (mg), given as a solution by mouth once a week.

A matching **placebo** solution given by mouth once a week

None of the participants, researchers, 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 ensure that the results are looked at fairly across all treatments.

What happened during the trial?

Before treatment — Up to one and a half months

Trial doctors checked participants' overall health and confirmed the presence of **Huntington's disease (HD)** to ensure they could be in this trial.

During treatment — 4 months

26 participants joined **Treatment Period 1** of this trial.

Participants were randomly assigned to 1 of the 2 groups using a computer:

LMI070: **21 participants**

- Participants received **LMI070** 56 mg solution by mouth once a week

Placebo: **5 participants**

- Participants received a **placebo** solution by mouth once a week

Researchers performed nerve function tests on participants to monitor for any nerve damage and checked their general health throughout the trial.

After treatment — Up to 1 year

Researchers continued to monitor the participants' health and symptoms with scheduled check ups and assessments for up to 1 year (approximately 4 visits) after their last dose.

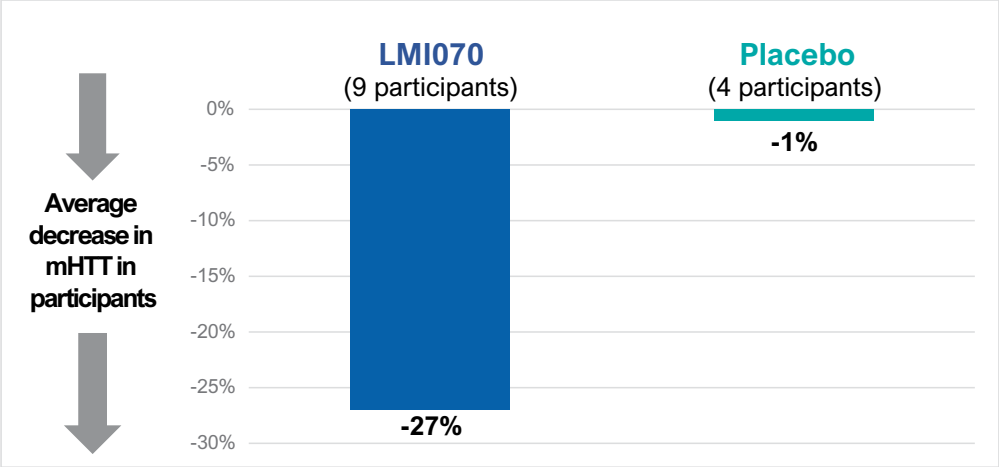
What were the main results of this trial?

What was the change in the levels of mHTT protein in the cerebrospinal fluid (CSF) of the participants after 16 weeks of treatment with LMI070 as compared to placebo?

After 16 weeks of treatment, **mHTT** protein levels were reduced by **27%** in the participants who were given **LMI070** and by **1%** in the participants who were given **placebo** compared to the start of the trial.

To answer this question, researchers collected and tested the samples of participants' **CSF** to measure the levels of **mHTT** in their **CSF**.

Percent change in the levels of mHTT protein in the CSF after 16 weeks of treatment



What adverse events did 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.

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.

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 treatment up to 1 year after taking the last dose of the trial treatment.

20 out of 26 participants had adverse events. 4 participants had adverse events that were considered serious. None of the participants left the trial or died due to an adverse event. This trial was stopped early because of safety concerns with the use of **LMI070**.

How many participants had adverse events?

Participants who:	LMI070 (21 participants)	Placebo (5 participants)
Had at least 1 serious adverse event	**4 of 21** 19%	**0**
Had at least 1 other adverse event	**18 of 21** 86%	**2 of 5** 40%

What serious adverse events did the participants have?

The table below shows the serious adverse events that happened during this trial.

	LMI070 (21 participants)	Placebo (5 participants)
Bleeding inside the head Subdural haematoma	**2 of 21** 10%	**0**
Growth in the inner lining of the uterus Uterine polyp	**1 of 21** 5%	**0**
Inflammation of the nerve in the inner ear due to an infection Vestibular neuronitis	**1 of 21** 5%	**0**

What other adverse events did the participants have?

20 participants had other adverse events. The table below shows the other adverse events that happened in at least **10%** of participants in any group.

	LMI070 (21 participants)	**Placebo** (5 participants)
A mental state associated with having false beliefs Delusional disorder, persecutory type	**0**	**1 of 5** 20%
Abnormal sensations under the skin Paraesthesia	**2 of 21** 10%	**1 of 5** 20%
COVID-19 infection	**2 of 21** 10%	**1 of 5** 20%
Headache	**2 of 21** 10%	**1 of 5** 20%
Inflammation in the bladder Cystitis	**3 of 21** 14%	**0**
Low levels of red blood cells Anemia	**4 of 21** 19%	**1 of 5** 20%
Nerve damage in brain and spinal cord Polyneuropathy	**3 of 21** 14%	**0**
Pain in mouth and throat Oropharyngeal pain	**0**	**1 of 5** 20%
Pain in the area where a needle was inserted Puncture site pain	**3 of 21** 14%	**0**
Urinary tract infection	**3 of 21** 14%	**0**

What was learned from this trial?

Researchers planned to find a safe and effective dose of **LMI070** for people with **Huntington's disease (HD)**. However, this trial was stopped early due to safety concerns. Therefore, researchers could not determine its overall effectiveness.

The researchers found that:

- **LMI070** at a dose of 56 mg lowered **mHTT** protein levels in **CSF** after 16 weeks of treatment compared to **placebo**. This was the first time an oral HTT-lowering drug showed a reduction in **mHTT** protein levels in the **CSF**.
- Some participants who received **LMI070** showed signs or symptoms of **peripheral neuropathy**. But all participants who had reported those signs or symptoms, experienced partial or complete recovery by the end of the last visit.

When this summary was written, there were no plans for future trials with **LMI070** in people with **HD**.

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 **NCT05111249**
- **clinicaltrialsregister.eu/ctr-search/search** - search using the number **2020-000105-92**

Other trials will appear on the public websites above. When there, search for **LMI070** or branaplam

Full clinical trial title: A randomized, double-blind, placebo-controlled dose range finding study with open-label extension to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of LMI070/branaplam when administered as weekly oral doses in participants with early manifest Huntington's disease

NOVARTIS

Novartis is a global healthcare company based in Switzerland that provides solutions to address the evolving needs of patients worldwide.

1-888-669-6682 (US) | +41-61-324 1111 (EU)

www.novartis.com/clinicaltrials