NOVARTIS

Clinical Trial
Results Summary

A clinical trial to learn about the effects of HDM201 in combination with azacitidine and venetoclax in people with acute myeloid leukemia

Thank you!

Thank you to the participants who took part in the clinical trial for **acute myeloid leukemia**. Every participant helped the researchers learn more about the trial drug **HDM201**, also called **siremadlin**.

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: CHDM201I12201

Novartis drug studied: **HDM201**, also called **siremadlin**

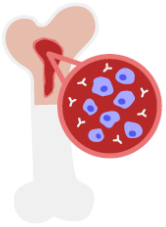
Sponsor: Novartis

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 **HDM201** in combination with **azacitidine** and **venetoclax** in people with **acute myeloid leukemia (AML)** who cannot receive intensive chemotherapy.



Acute myeloid leukemia (AML) is a blood cancer that starts in myeloid cells that are present in the bone marrow. Bone marrow is the tissue inside bones that helps make blood cells. Usually, myeloid cells develop into mature (fully developed and normal) blood cells such as red blood cells (cells that transport oxygen) , white blood cells (cells that protect the body against infections), and platelets (cells that help blood clot). In people with **AML**, these myeloid cells develop into abnormal blood cells (not fully developed, also called immature) that do not function properly. Common symptoms of **AML** are tiredness, weakness, frequent infections, fever, easy bruising, and bleeding.

Intensive chemotherapy is a treatment option for **AML**, but it is not suitable for elderly people and/or those with other health issues, as it can cause severe complications. Those who were unable to receive intensive chemotherapy, according to their doctors, are called **AML unfit**. Researchers are looking for treatment options that can help people who are **AML unfit**.

HDM201, also called **siremadlin**, is a trial drug that aims to block a protein involved in the growth of cancer cells. By blocking this protein, researchers think it may treat certain types of cancers, including **AML**.

In this trial, participants also received **azacitidine** and **venetoclax**, along with **HDM201**. **Azacitidine** and **venetoclax** are approved treatments for **AML** in some countries. These medicines work by blocking the growth of cancer cells.

Trial drug
HDM201 also called **siremadlin**
Pronounced as
sie-ur-mad-lin

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

- What was the best dose of **HDM201** in combination with **azacitidine** and **venetoclax** in participants with **AML**?
- How many participants had **complete remission** after treatment with the best dose of **HDM201** in combination with **azacitidine** and **venetoclax**?
- What medical problems, also called adverse events, happened during this trial?

  Adverse events reported in this trial were any sign or symptom that participants had during the trial. Adverse events **may** or **may not** be caused by treatments in the trial.

In this trial, a participant was considered to have **complete remission** when:

- The bone marrow has less than 5% immature blood cells
- The blood has normal levels of neutrophils (a type of white blood cell) and platelets, and no immature blood cells are present
- There are no signs of the disease outside the bone marrow, such as in the brain or soft tissues

How long was this trial?

This trial began in May 2022. It was planned that participants would continue the trial treatment for as long as they continued to benefit from the treatment. However, the trial ended earlier than planned in April 2024. The sponsor decided to end the trial early due to a business decision and not because of any safety concerns during the trial.

This trial was designed to have 2 parts:

- **Part 1** was to find the best dose of **HDM201** in combination with **azacitidine** and **venetoclax** that would be used in Part 2 of the trial. This was to be done by assessing the safety of different doses of **HDM201** during the trial. However, researchers could test only one dose level of **HDM201** before the trial stopped.
- **Part 2** was to further assess the effects of the best dose of **HDM201** in combination with **azacitidine** and **venetoclax** in larger groups of participants. However, **Part 2** did not start as the trial ended earlier than planned.

Even though the trial stopped early, Novartis was committed to providing a full report of the available trial results. This summary is based on that report.

Who was in this trial?

During **Part 1**, 14 participants with **unfit AML** joined this trial: 7 men and 7 women. Participants' ages ranged from 47 to 79 years.

The number of participants by race is shown below.

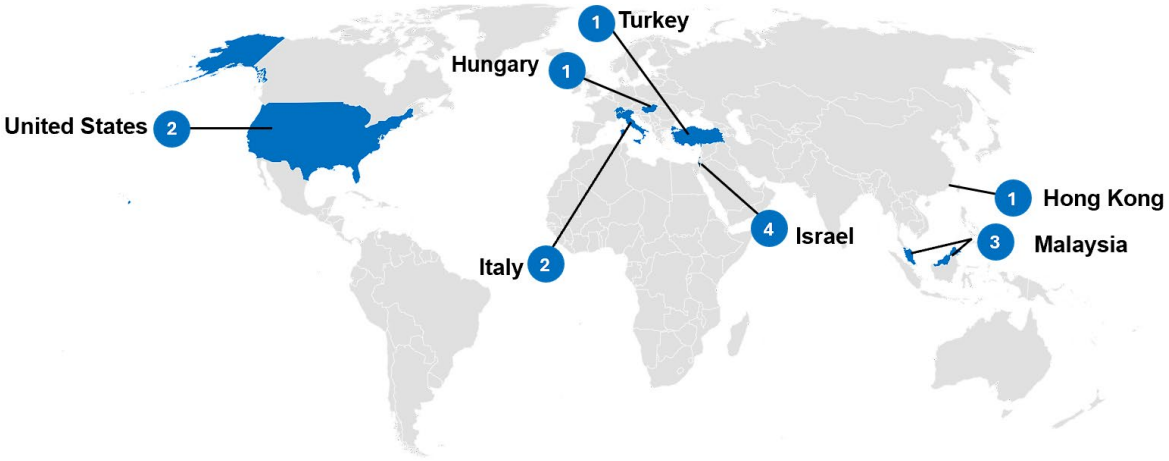
Race

4 Asian	10 White

The participants could take part in this trial if they:

- were more than 18 years old
- had **unfit AML** (people with **AML** who could not receive intensive chemotherapy)
- did not have certain gene defects
- were either fully active or at least able to do their daily jobs, except for heavy activities

14 participants* from 7 countries took part in this trial. The map below shows the number of participants who took part in each country.



*14 participants received the treatment, and later, 1 participant was excluded from the trial (due to a gene defect).

What treatments did the participants receive?

The treatments in this trial were:

HDM201: Participants took 20 milligrams (the only dose tested) as a capsule by mouth on an empty stomach for the first 5 days of a 28-day treatment cycle.

Azacitidine: Participants received this as an infusion into a vein or as an injection under the skin for the first 7 days of the 28-day treatment cycle.

Venetoclax: Participants took this as a tablet by mouth daily during the 28-day treatment cycle.

A **cycle** is a treatment period that is repeated until the treatment is discontinued.

In this trial, each cycle lasted for 28 days (roughly one month).

This was an open-label trial, which means each participant, the trial doctors, and the trial staff knew what treatment participants were receiving.

What happened during this trial?

Before treatment

Up to 1 month

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

During treatment

As long as participants continued to benefit from treatment

All participants received **HDM201** with **azacitidine** and **venetoclax**

Part 1: 14 participants* with unfit AML received treatment in 2 groups:

Group 1 (Unfit AML who received previous treatment): **6 participants**

Participants with unfit AML who had received previous treatment with **azacitidine** and **venetoclax** before this trial but did not respond as expected.

Group 2 (Newly diagnosed unfit AML): **8* participants**

Participants who were newly diagnosed, had never received any treatment for AML and were less likely to benefit from other anti-cancer treatments.

*1 participant from Group 2 received treatment but was later found ineligible to be included (due to a gene defect) and was not included in the main results of this trial.

Part 2: This part of the trial did not start as the trial ended earlier than planned.

After treatment

Up to 1 month

Trial staff checked participants' general health and for any medical problems for up to a month after a participants' last dose of trial treatment.

What were the main results of this trial?

What was the best dose of HDM201 in combination with azacitidine and venetoclax in participants with AML?

Researchers could not identify the best dose of **HDM201** in combination with **azacitidine** and **venetoclax**, as the trial ended earlier than planned.

To find the **best dose**, researchers planned to monitor the participants' health and record the number of participants who had any dose-limiting toxicities (DLTs) for each dose tested during their first treatment cycle. However, the researchers could not test different doses to identify the best dose as the trial ended earlier than planned.

What are dose-limiting toxicities (DLTs)?

DLTs are medical problems that:

- The trial doctors think could be related to the trial treatment
- Lead to a pause in, or lowering of the dose of, treatment

10 participants were included in the DLT results. To be included in the DLT results, participants had to complete the first treatment cycle, receive an appropriate dose of the trial treatment, and have available results to report.

In **Group 1**, no participants experienced a DLT. In **Group 2**, 1 out of 7 participants experienced a DLT of **severe immune response to an infection** (sepsis).

	Group 1 Unfit AML who received previous treatment 3 participants	Group 2 Newly diagnosed unfit AML 7 participants
DLT	**0 of 3**	**1 of 7** **14%**

How many participants had complete remission after treatment with the best dose of HDM201 in combination with azacitidine and venetoclax?

Researchers could not evaluate this result as the trial ended earlier than planned.

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 the treatment until a month after receiving the last dose of **HDM201**.

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.

All the treated participants had adverse events. 13 of 14 participants had adverse events that were considered serious. None of the participants left the trial due to an adverse event. 5 participants died. Researchers concluded there were no new safety concerns for **HDM201** in this trial.

How many participants had adverse events?

	Group 1 Unfit AML who received previous treatment 6 participants	Group 2 Newly diagnosed unfit AML 8 participants*
Had at least 1 **serious adverse event**	**6 of 6**	**7 of 8**
Had at least 1 **other** (not including serious) **adverse event**	**5 of 6**	**8 of 8**
Died	**1 of 6**	**4 of 8**

What serious adverse events did the participants have?

The table below shows the most common serious adverse events that happened in this trial:

	Group 1 Unfit AML who received previous treatment 6 participants	Group 2 Newly diagnosed unfit AML 8 participants*
Fever with a low number of neutrophils, a type of white blood cell Febrile Neutropenia	**2 of 6** 33%	**3 of 8** 38%
Severe infection due to low number of neutrophils Neutropenic sepsis	**0**	**2 of 8** 25%
Severe infection leading to low blood pressure Septic shock	**0**	**2 of 8** 25%
Severe infection throughout the body Sepsis	**0**	**2 of 8** 25%

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

The table below shows the most common other adverse events that happened in this trial:

	Group 1 Unfit AML who received previous treatment 6 participants	Group 2 Newly diagnosed unfit AML 8 participants
Diarrhea	**3 of 6** 50%	**2 of 8** 25%
Feeling sick Nausea	**3 of 6** 50%	**3 of 8** 38%
Feeling weak with no energy Asthenia	**2 of 6** 33%	**2 of 8** 25%
Low level of blood platelets, cells that help blood to clot Thrombocytopenia	**1 of 6** 17%	**6 of 8** 75%
Low levels of potassium in the blood Hypokalemia	**1 of 6** 17%	**4 of 8** 50%
Low neutrophils, a type of white blood cells Neutropenia	**2 of 6** 33%	**5 of 8** 63%
Low red blood cells Anemia	**2 of 6** 33%	**3 of 8** 38%
Reduced appetite	**2 of 6** 33%	**0**
Vomiting	**1 of 6** 17%	**3 of 8** 38%

What was learned from this trial?

Researchers wanted to learn about the effects of **HDM201** in combination with **venetoclax** and **azacitidine** in people with **unfit acute myeloid leukemia (AML)**.

- The best dose of **HDM201** in combination with **azacitidine** and **venetoclax** could not be identified as the trial ended earlier than planned.
- There were no new safety concerns in the trial.

When this summary was written, the sponsor had no plans for future trials of **HDM201** in people with **unfit AML**.

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 accept** → Search for **CHDM201I12201**

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

- clinicaltrials.gov– search using the number **NCT05155709**
- clinicaltrialsregister.eu/ctr-search/search - search using the number **2021-001165-21**

Other trials of **HDM201** may appear on the public websites above. When there, search for **HDM201** or **siremadlin**.

Full clinical trial title: A phase Ib/II open label dose confirmation, proof of concept study of siremadlin in combination with venetoclax plus azacitidine in unfit adult AML participants who responded sub-optimally to first-line venetoclax plus azacitidine treatment and in participants with newly diagnosed unfit AML presenting with high-risk clinical features

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