NOVARTIS

Clinical Trial Results Summary

A clinical trial to learn more about the effects of HDM201 in combination with MBG453 or venetoclax in people with acute myeloid leukemia or high-risk myelodysplastic syndrome

Thank you!

Thank you to the participants who took part in the clinical trial for **acute myeloid leukemia (AML)** and **high-risk myelodysplastic syndrome (MDS)**. Every participant helped the researchers learn more about the trial drugs **HDM201**, also called **siremadlin**, **MBG453**, also called **sabatolimab**, and **venetoclax**.

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: CHDM201H12101C

Novartis drug studied: **HDM201** (**siremadlin**), **MBG453** (**sabatolimab**), and **venetoclax**

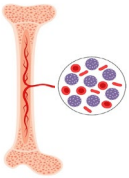
Sponsor: Novartis

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 **MBG453** or **venetoclax** in people with **acute myeloid leukemia (AML)** or **high-risk myelodysplastic syndrome (MDS)**.



AML is a fast-growing cancer that starts in the bone marrow—the spongy tissue inside bones where blood cells are made. It affects the cells that normally turn into blood cells, especially white blood cells. The cancer cells build up and slow down the making of normal blood cells. Common symptoms of **AML** are tiredness, weakness, frequent infections, fever, easy bruising, and bleeding. **MDS** is a group of conditions where the blood cells formed in the bone marrow do not mature and become healthy. The symptoms of **MDS** include weakness, shortness of breath, pale skin, bleeding, being more prone to infections, and red or purple spots on the skin. In some cases, **MDS** might progress to **AML**.

HDM201, also called **siremadlin**, is a trial drug that aims to block a protein called MDM2 involved in the growth of cancer cells. By blocking this protein, researchers think it may treat certain types of cancer, including **AML**.

MBG453, also called **sabatolimab**, is currently being studied for **high-risk MDS**. It works by blocking a protein called TIM-3 present on the surface of some white blood cells and cancer cells. This process activates the immune system and reduces the growth of cancer cells.

Venetoclax is a drug approved for the treatment of **AML** in some countries. It works by blocking a protein called BCL-2, that prevents cancer cells from being destroyed.

Trial drugs
HDM201, also called **siremadlin**

Pronounced as
sie-ur-mad-lin
MBG453, also called sabatolimab
Pronounced as
Saba-To-li-mab

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

- What were the best doses of **HDM201** in combination with **MBG453** or **venetoclax** for participants?
- What medical problems, also called adverse events, happened 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.

How long was this trial?

The trial began in June 2019. 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 August 2024.

The sponsor decided to end the trial early due to business decisions. This decision was not related to any safety concerns during the trial.

This trial was designed to have 2 groups:

- Group 1 looked at the safety of increasing doses of **HDM201** in combination with **MBG453** to find the best dose of **HDM201** for this combination to give to participants.
- **Group 2** looked at the safety of increasing doses of **HDM201** in combination with **venetoclax** to find the best dose of **HDM201** for this combination to give to participants.

Who was in this trial?

52 participants with **AML** or **high-risk MDS** received treatment in this trial. Participants were divided into 2 treatment groups: Group 1 and **Group 2**.

There were 17 participants in Group 1 – 12 men and 5 women. The participants' ages ranged from 57 to 79 years. Their average age was 68 years.

There were 35 participants in **Group 2** – 16 men and 19 women. The participants' ages ranged from 21 to 84 years. Their average age was 67 years.

The number of participants by race in Group 1 and **Group 2** is shown below.

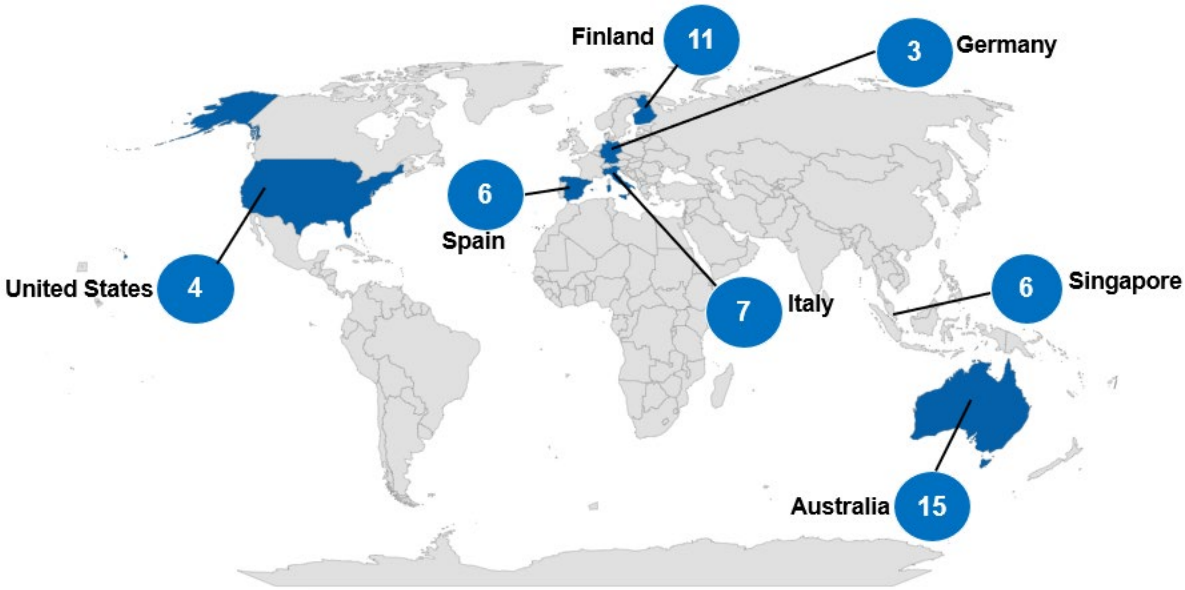
Race	Group 1
Asian	2
White	15

Race	Group 2
Asian	4
White	31

The participants could take part in this trial if they:

- were at least 18 years of age
- had **AML** that returned or did not respond to previous treatments, and could not receive standard treatment as confirmed by the study doctor
- were newly diagnosed with **AML**, and could not receive standard treatment or live in a country where no approved therapies for **AML** are available
- had **high-risk MDS** that could not be treated with hypomethylating agents (a type of medicine used to treat certain cancers)
- were fully active, and able to walk or carry out light work

52 participants from 7 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 given in **cycles**.

The participants received the following treatments:

HDM201: Participants took **HDM201** once daily as capsules by mouth on an empty stomach for the first 5 days of a 28-day treatment cycle.

This trial looked at 4 doses of **HDM201**:

- 20 milligrams (mg)
- 30 mg
- 40 mg
- 60 mg

MBG453: Participants received **MBG453** as an infusion into a vein on Days 1 and 15 of the 28-day treatment cycle.

This trial looked at 2 doses of **MBG453**:

- 400 mg
- 800 mg

Venetoclax: Participants gradually increased their dose of **venetoclax** over 4 days to a maximum of 400mg. Participants took 400 mg of **venetoclax** as a tablet by mouth daily during the 28-day treatment cycle.

What is a cycle?

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

In this trial, each **cycle** lasted for 28 days.

In this trial, the participants, the trial doctors, and the trial staff knew what treatments participants were receiving.

The participants could continue trial treatment as long as they were benefiting from it or until they stopped participating in the trial for any reason.

What happened during this trial?

Before treatment

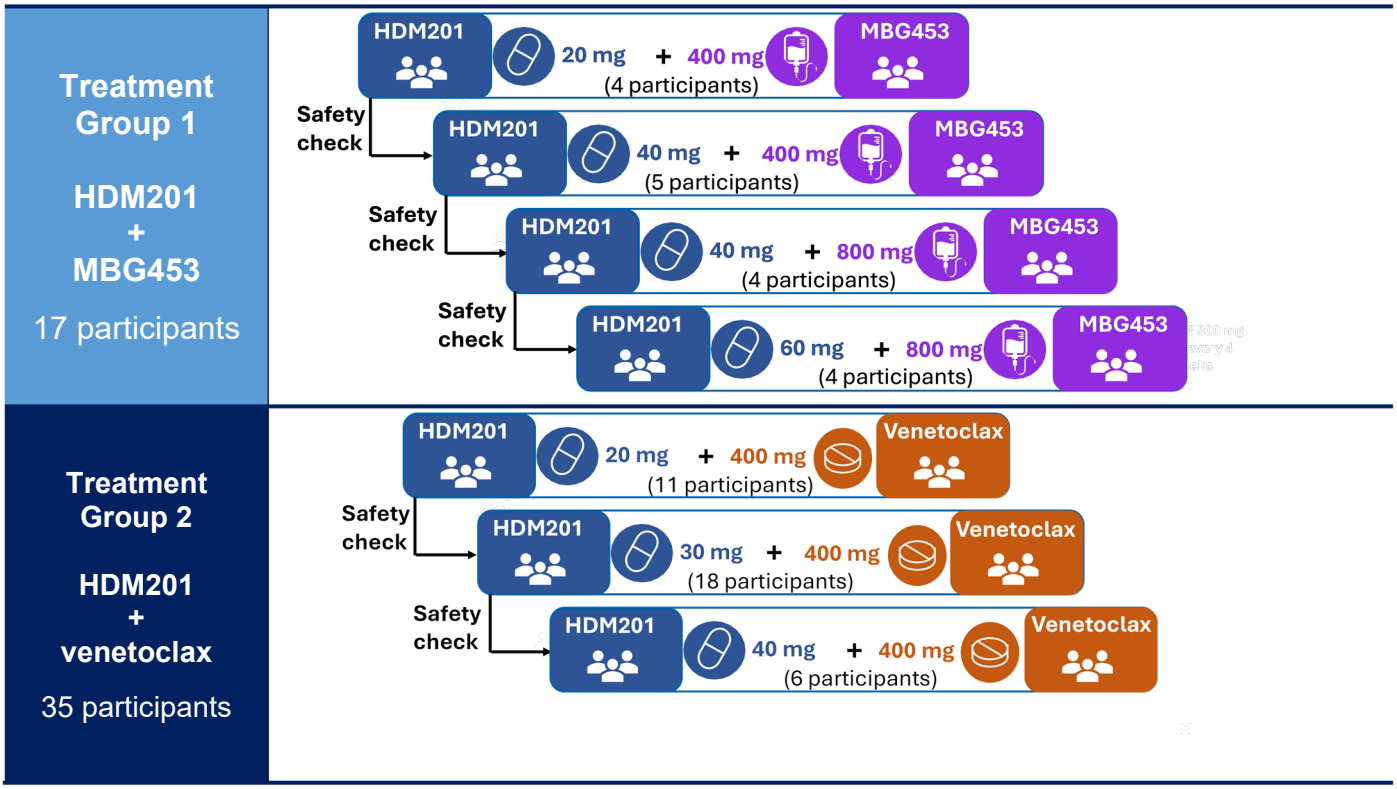
Up to 21 days

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

Participants were assigned to the following treatment groups:



Researchers started by giving lower doses of **HDM201** along with 2 doses of **MBG453 (Group 1)** or a single dose of **venetoclax (Group 2)** to a few participants. Researchers checked the safety of the lower dose of **HDM201** before giving the higher dose to the next group of participants. This continued until the safety of each dose was assessed.

After treatment

Up to 5 months

After the last dose of a participant's trial treatment, trial staff checked their general health and monitored for any medical problems for:

- about 5 months for **Group 1** participants
- about 1 month for **Group 2** participants

What were the main results of this trial?

What were the best doses of HDM201 in combination with MBG453 or venetoclax for participants?

- In Group 1, researchers could not identify the best dose of **HDM201** in combination with **MBG453** as the trial stopped earlier than planned.
- In **Group 2**, researchers identified **30 mg** of **HDM201** (given on the first 5 days of each treatment cycle) as the best dose in combination with 400 mg **venetoclax** for **AML** participants.

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.

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

None of the participants in Group 1 experienced any **DLTs**.

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

The tables below show how many participants had **DLTs** in **Group 2**.

	Group 2		
	HDM201 (20 mg) + Venetoclax (400 mg) 7 participants	**HDM201 (30 mg) + Venetoclax (400 mg)** 16 participants	**HDM201 (40 mg) + Venetoclax (400 mg)** 5 participants
DLTs	**1 of 7** 14%	**2 of 16** 13%	**0**

The **DLTs** observed in **Group 2** were:

- low red blood cell count
- bone marrow unable to make healthy blood cells
- fever with a low number of neutrophils, a type of white blood cell
- low level of blood platelets, cells that help blood to clot

A participant in **Group 2** could have more than one **DLT**.

The table below shows how many participants had to receive lowered doses or pause their trial drugs during treatment.

Group 1
17 participants

	HDM201 (20 mg) + MBG453 (400 mg) 4 participants	HDM201 (40 mg) + MBG453 (400 mg) 5 participants	HDM201 (40 mg) + MBG453 (800 mg) 4 participants	HDM201 (60 mg) + MBG453 (800 mg) 4 participants
Lowered the dose of HDM201	0	0	0	0
Paused HDM201	3 of 4 75%	2 of 5 40%	2 of 4 50%	0
Lowered the dose of MBG453	0	0	0	0
Paused MBG453	1 of 4 25%	3 of 5 60%	2 of 4 50%	0

Group 2
35 participants

	HDM201 (20 mg) + Venetoclax (400 mg) 11 participants	HDM201 (30 mg) + Venetoclax (400 mg) 18 participants	HDM201 (40 mg) + Venetoclax (400 mg) 6 participants
Lowered the dose of HDM201	0	1 of 18 6%	0
Paused HDM201	7 of 11 64%	11 of 18 61%	2 of 6 33%
Lowered the dose of Venetoclax	1 of 11 9%	2 of 18 11%	1 of 6 17%
Paused Venetoclax	8 of 11 73%	12 of 18 67%	3 of 6 50%

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:

- 5 months after the last treatment for **Group 1** participants
- 1 month after the last treatment for **Group 2** 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.

- All the participants (17 of 17) in **Group 1** and (35 of 35) in **Group 2** had adverse events.
- 17 participants in **Group 1** and 26 participants in **Group 2** had adverse events that were considered serious.
- 13 participants in **Group 1** and 9 participants in **Group 2** died due to any cause, including **AML** or **high-risk MDS**.
- 1 participant in **Group 1** and 9 participants in **Group 2** left the trial due to an adverse event.
- The researchers concluded there were no new safety concerns for **HDM201**, **MBG453** or **venetoclax** in this trial.

How many participants had adverse events?

Group 1
17 participants

	HDM201 (20 mg) + MBG453 (400 mg) 4 participants	HDM201 (40 mg) + MBG453 (400 mg) 5 participants	HDM201 (40 mg) + MBG453 (800 mg) 4 participants	HDM201 (60 mg) + MBG453 (800 mg) 4 participants
Had at least 1 **serious adverse event**	4 of 4 100%	5 of 5 100%	4 of 4 100%	4 of 4 100%
Left the trial due to an adverse event	1 of 4 25%	0	0	0
Died due to any cause	3 of 4 75%	3 of 5 60%	3 of 4 75%	4 of 4 100%

Group 2
35 participants

	HDM201 (20 mg) + Venetoclax (400 mg) 11 participants	HDM201 (30 mg) + Venetoclax (400 mg) 18 participants	HDM201 (40 mg) + Venetoclax (400 mg) 6 participants
Had at least 1 **serious adverse event**	8 of 11 73%	14 of 18 78%	4 of 6 67%
Left the trial due to an adverse event	2 of 11 18%	3 of 18 17%	4 of 6 67%
Died due to any cause	3 of 11 27%	2 of 18 11%	4 of 6 67%

What serious adverse events did the participants have?

17 participants in **Group 1** and 26 participants in **Group 2** had serious adverse events.

The table below shows the most common serious adverse events that happened in **Group 1** and **Group 2**.

Group 1
17 participants

	HDM201 (20 mg) + MBG453 (400 mg) 4 participants	HDM201 (40 mg) + MBG453 (400 mg) 5 participants	HDM201 (40 mg) + MBG453 (800 mg) 4 participants	HDM201 (60 mg) + MBG453 (800 mg) 4 participants
Fever with a low number of neutrophils, a type of white blood cell Febrile neutropenia	1 of 4 25%	1 of 5 20%	1 of 4 25%	2 of 4 50%
Increased number of white blood cells Leukocytosis	0	0	2 of 4 50%	0
Fever Pyrexia	0	1 of 5 20%	3 of 4 75%	0
Lung infection Pneumonia	0	2 of 5 40%	1 of 4 25%	1 of 4 25%
Serious complication of an infection Sepsis	2 of 4 50%	1 of 5 20%	1 of 4 25%	0

Group 2
35 participants

	HDM201 (20 mg) + Venetoclax (400 mg) 11 participants	HDM201 (30 mg) + Venetoclax (400 mg) 18 participants	HDM201 (40 mg) + Venetoclax (400 mg) 6 participants
Fever with a low number of neutrophils, a type of white blood cell Febrile neutropenia	5 of 11 45%	8 of 18 44%	1 of 6 17%
Serious complication of an infection Sepsis	0	0	2 of 6 33%

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

The table below shows the most common other adverse events that happened in **Group 1** and **Group 2**.

Group 1
17 participants

	HDM201 (20 mg) + MBG453 (400 mg) 4 participants	HDM201 (40 mg) + MBG453 (400 mg) 5 participants	HDM201 (40 mg) + MBG453 (800 mg) 4 participants	HDM201 (60 mg) + MBG453 (800 mg) 4 participants
Low number of red blood cells Anemia	3 of 4 75%	3 of 5 60%	2 of 4 50%	1 of 4 25%
Low number of platelets (cells that help blood to clot) Thrombocytopenia	0	1 of 5 20%	1 of 4 25%	3 of 4 75%
Nausea	3 of 4 75%	1 of 5 20%	3 of 4 75%	3 of 4 75%
Vomiting	0	1 of 5 20%	3 of 4 75%	1 of 4 25%

Group 2
35 participants

	HDM201 (20 mg) + Venetoclax (400 mg) 11 participants	HDM201 (30 mg) + Venetoclax (400 mg) 18 participants	HDM201 (40 mg) + Venetoclax (400 mg) 6 participants
Diarrhea	5 of 11 45%	9 of 18 50%	4 of 6 67%
Nausea	8 of 11 73%	10 of 18 56%	3 of 6 50%

What was learned from this trial?

Researchers learned about the effects of **HDM201** in combination with **MBG453** or **venetoclax** in people with **acute myeloid leukemia (AML)** or **high-risk myelodysplastic syndrome (MDS)**.

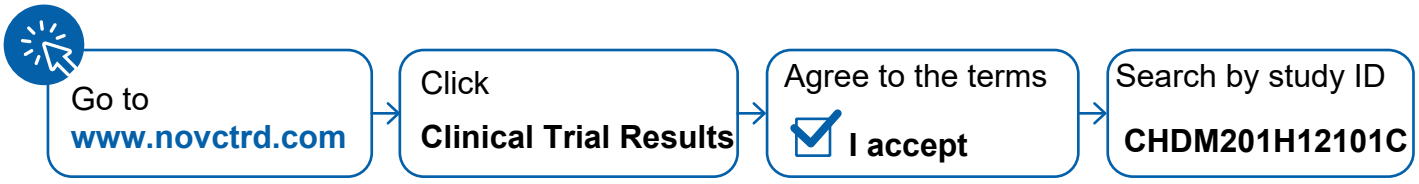
- This trial ended earlier than planned due to business decisions. This decision was not related to any safety concerns during the trial.
- The researchers could not identify the best dose of **HDM201** in combination with **MBG453**. The researchers identified **30 mg** of **HDM201** as the best dose in combination with **venetoclax** for **AML** participants.
- The researchers concluded that there were no new safety concerns for **HDM201**, **MBG453** or **venetoclax** in this trial.

When this summary was written, the sponsor had no plans for future trials of **HDM201**, **MBG453** or **venetoclax** in people with **acute myeloid leukemia** and **high-risk myelodysplastic syndrome**.

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 **NCT03940352**
- clinicaltrialsregister.eu/ctr-search/search– search using the number **2018-004001-62**

Other trials of **HDM201**, **MBG453**, and **venetoclax** may appear on the public websites above. When there, search for **HDM201** or **siremadlin**, **MBG453** or **sabatolimab**, or **venetoclax**.

Full clinical trial title: A phase Ib, multi-arm, open-label, study of HDM201 in combination with MBG453 or venetoclax in adult subjects with acute myeloid leukemia (AML) or high-risk myelodysplastic syndrome (MDS)

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

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