NOVARTIS

Clinical Trial Results Summary

A Study to Learn About the Effects of Midostaurin in People With *FLT3*-Mutated Acute Myeloid Leukemia (AML)

Thank you!

Thank you to the participants who took part in the clinical trial for AML. Every participant helped the researchers learn more about **midostaurin**.

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: CPKC412A2220
Drug studied: Midostaurin (PKC412)
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.

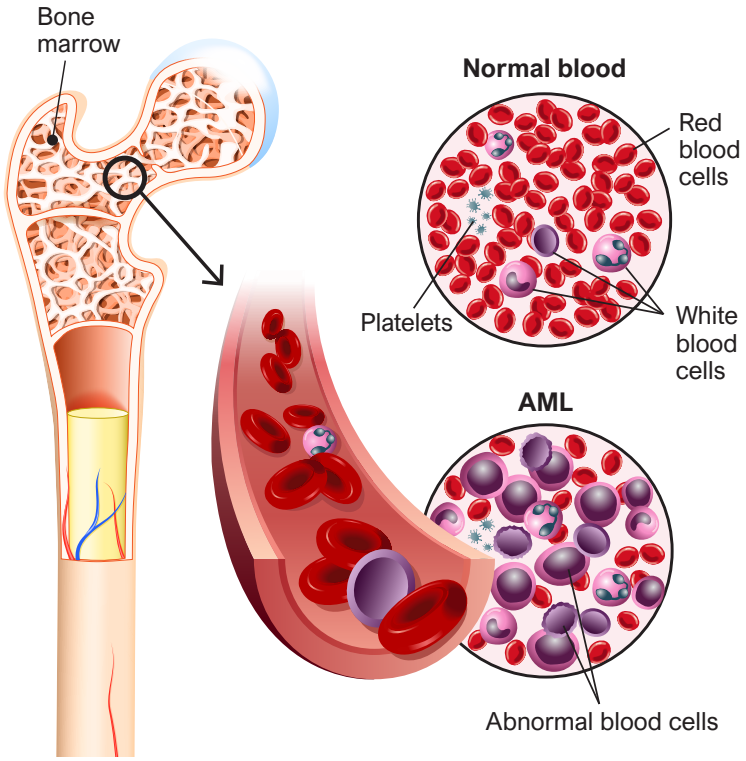
This summary only shows the results of a single clinical trial. Other clinical trials may have different findings.

What was the main purpose of this trial?

Acute myeloid leukemia (AML) is a cancer of blood cells that starts in the bone marrow. Bone marrow is a soft, spongy tissue found in the center of most bones where new blood cells are made. AML affects a group of blood cells called the **myeloid cells**, which normally develop into mature blood cells such as red blood cells, white blood cells and platelets. In people with AML, these myeloid cells develop into abnormal blood cells that do not function properly.

Common symptoms of AML are tiredness, weakness, frequent infections, fever, and easy bruising and bleeding. AML that is left untreated can spread and get worse quickly.

One of the main causes of AML is a mutation in a gene called FMS-like tyrosine kinase receptor-3, or ***FLT3.*** A mutation is a change in the gene's structure which affects its normal function. The normal *FLT3* gene provides instructions to form FLT3 proteins which help the myeloid cells develop into healthy blood cells.



Chemotherapy uses medicines to kill cancer cells or stop them from growing and dividing. The usual treatment for AML is chemotherapy that uses 2 drugs called **daunorubicin** and **cytarabine**. While chemotherapy can prove effective at first, AML tends to return over time. Long-term survival rates are low even after chemotherapy. Researchers are looking for new treatments that can help keep people with AML stay in remission longer. Remission means that signs and symptoms of cancer are reduced.

The trial drug, **midostaurin**, blocks abnormal FLT3 proteins. When used in combination with other drugs, it may stop cancer cells from spreading and work longer than just chemotherapy. Midostaurin is approved in the United States and the European Union for the treatment of *FLT3*-mutated AML.

In this trial, researchers wanted to further study the effects of midostaurin when given in combination with standard chemotherapy. Part 1 of the study tested the safety of midostaurin in Japan only, where it is not yet approved for AML.

The main questions that researchers wanted to answer were:

- **Part 1:** How many participants stopped treatment due to midostaurin-related serious adverse events or death?
- **Part 2:** How long did participants have an event-free survival?
  - ↳ **Event-free survival** measures the time from the start of treatment until certain key events happen. These events include the cancer not getting better with treatment, the cancer coming back after treatment, or the participant dying.
- What adverse events did participants have during this trial?
  - ↳ An **adverse event** is any sign or symptom that participants have during a trial.

How long was this trial?

The trial began in April 2018 and ended in November 2022. The entire duration of the trial was about 5 years.

When the trial ended, researchers created a report of the trial results. This summary is based on that report.

Who was in this trial?

67 participants with AML took part in the trial, and 66 participants received treatment. One participant in Part 2 did not receive treatment.
Participants' ages ranged from 22 to 70 years. Their average age was 47 years.

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

Gender

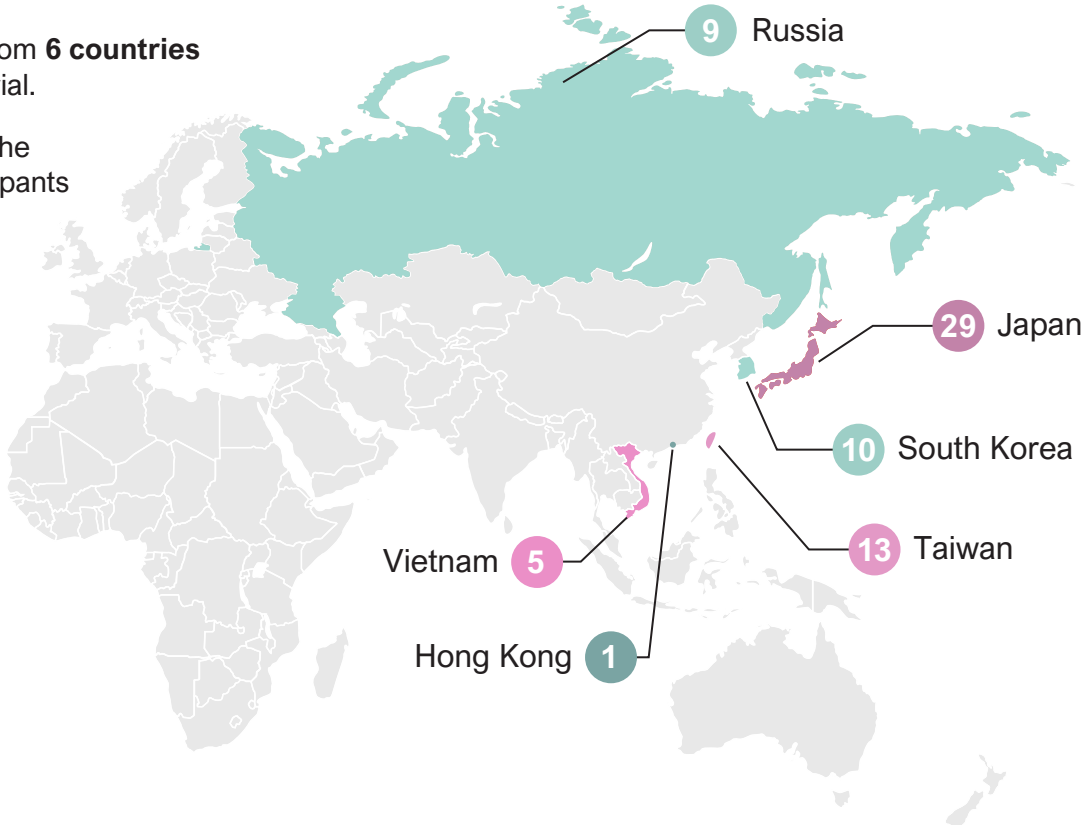
32 Men	35 Women

Race

57 Asian	9 White	1 Missing

67 participants from **6 countries** took part in the trial.

The map shows the number of participants who took part in each country.



Participants **could take part** in this trial if they:

- Were 18 to 70 years old
- Had AML
- Had a *FLT3* gene mutation (For Part 2 only)

Participants **could not take part** in this trial if they:

- Had spread of blood cancer into the brain or spinal cord.

What treatments did the participants receive?

Researchers studied the following treatments:

Midostaurin: 50 milligrams (mg), provided as capsules, taken by mouth twice a day.

Placebo: Looks like the trial drug but does not have any active drug in it. Using a placebo helps researchers better understand the effect of the trial drug.

The chemotherapy drugs that were given in combination with midostaurin and placebo were:

- **Cytarabine:** 100, 200, or 2000 milligrams per square meter (mg/m^2) per day, given as a slow injection into a vein.
- **Daunorubicin:** 50 or 60 mg/m^2 per day, given as an injection into a vein.

The exact dose for cytarabine and daunorubicin was based on each participant's body mass index (BMI). BMI is a measure of a person's body composition based on height and weight.

In this trial, the participants, trial doctors, and trial staff did not know whether the participants received midostaurin or placebo. 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?

The trial had **2 parts**.

Part 1

Part 1 of the trial took place in Japan only. 5 participants from Japan received midostaurin in addition to their regular chemotherapy treatment and were monitored for safety. Additional participants from Japan were enrolled after an independent committee reviewed and approved the safety results.

Part 2

Before treatment

Up to 7 days

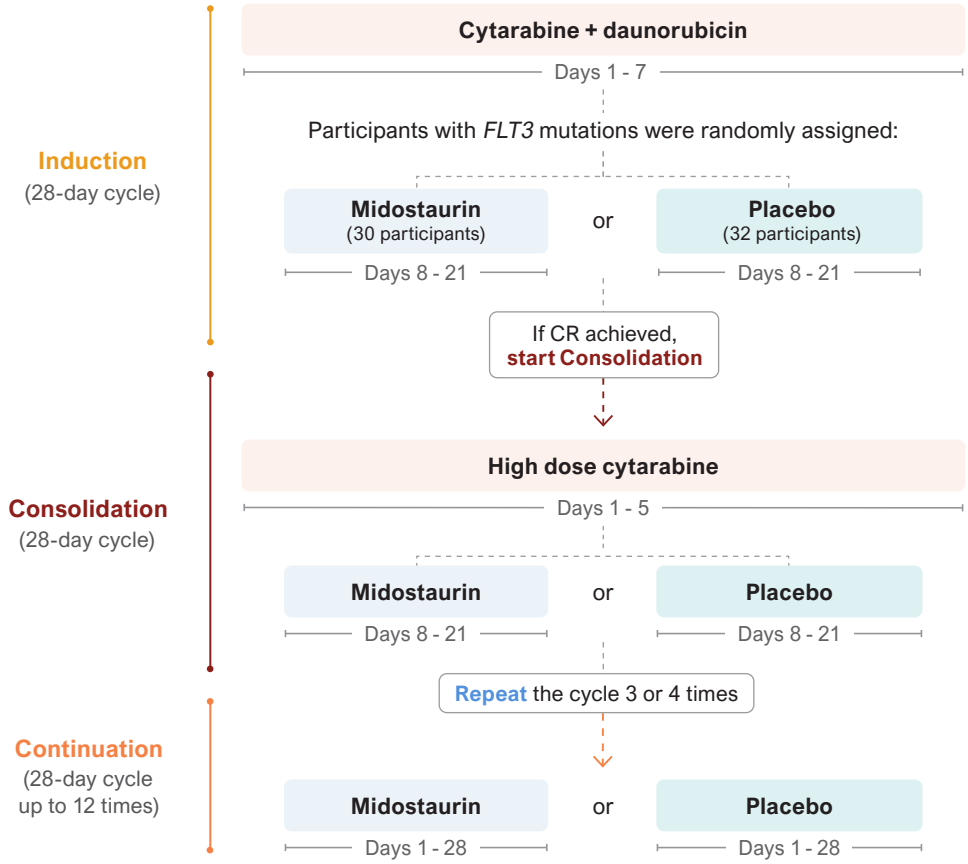
62 participants from different countries including Japan were included in Part 2. Participants had a physical exam and blood and urine tests. Researchers also collected bone marrow samples to check the growth of cancer cells and to confirm the FLT3 mutations.

During treatment

Up to 19 months

Participants received treatment in 3 different phases: **Induction**, **Consolidation**, and **Continuation**. Each phase had 28-day cycles. Participants only moved from one phase to the next if they had **complete remission (CR)**. CR meant that the cancer was under control with low levels of abnormal cells.

All participants received:



Participants stopped treatment if they had no CR after 2 cycles of **Induction** or at any point during **Consolidation** phase.

After treatment

Up to 2 years

Participants were:

- Checked for adverse events up to 30 days after their last dose.
- Checked for cancer relapse or death until the end of the trial.

What were the main results of this trial?

Part 1

How many participants stopped treatment due to midostaurin-related serious adverse events or death?

Researchers found that none of the participants stopped treatment due to midostaurin-related serious adverse events or death. Researchers closely monitored participants for adverse events until Day 21 of the 1st cycle of the consolidation phase.

Part 2

How long did participants have an event-free survival?

The event-free survival was 8 months for the 30 participants who took **midostaurin**. Event-free survival could not be calculated for the 32 participants in the **placebo** group.

Event-free survival measures the time from the start of treatment until certain key events happen. These events include the cancer not getting better with treatment, the cancer coming back after treatment, or the participant dying. Researchers checked event-free survival for as long as participants remained in the trial. The longest amount of time a participant was checked was 46 months.

As many participants left during the study, there were not enough events seen in the placebo group for researchers to calculate an event-free survival time. As a result, researchers concluded that event-free survival for participants who received midostaurin did not show an advantage over placebo.

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 during treatment, up to 30 days after the last dose of trial drug.

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 66 participants had adverse events:

- **24 participants** had adverse events that were considered serious.
- **20 participants** died due to adverse events.
- **12 participants** left the trial due to an adverse event.

The researchers concluded there were no new unexpected safety concerns for midostaurin for this trial.

How many participants had adverse events?

The table below shows how many participants who received treatment had adverse events.

Summary of adverse events

Participants who:	Part 1 Midostaurin 5 participants	Part 2 Midostaurin 30 participants	Part 2 Placebo 31 participants
Had at least 1 adverse event	5 of 5 **(100%)**	30 of 30 **(100%)**	31 of 31 **(100%)**
Had at least 1 serious adverse event	2 of 5 **(40%)**	12 of 30 **(40%)**	10 of 31 **(32%)**
Left the trial due to an adverse event	2 of 5 **(40%)**	4 of 30 **(13%)**	6 of 31 **(19%)**
Died during the trial	1 of 5 **(20%)**	3 of 30 **(10%)**	1 of 31 **(3%)**

What serious adverse events did the participants have?

A total of 24 participants who received at least 1 dose of trial drug had serious adverse events. The table below shows the serious adverse events that happened in at least 2 participants.

Serious adverse events

	Part 1 Midostaurin 5 participants	Part 2 Midostaurin 30 participants	Part 2 Placebo 31 participants
Lung infection Pneumonia	1 of 5 **(20%)**	5 of 30 **(17%)**	2 of 31 **(6%)**
Extreme immune response to an infection Sepsis	1 of 5 **(20%)**	3 of 30 **(10%)**	1 of 31 **(3%)**
Fever with low neutrophil count Febrile neutropenia	1 of 5 **(20%)**	2 of 30 **(7%)**	1 of 31 **(3%)**
Dangerously low blood pressure due to severe infection Septic shock	0 of 5 **(0%)**	2 of 30 **(7%)**	1 of 31 **(3%)**
Fever Pyrexia	0 of 5 **(0%)**	1 of 30 **(3%)**	2 of 31 **(6%)**
Low levels of blood platelets Thrombocytopenia	0 of 5 **(0%)**	1 of 30 **(3%)**	1 of 31 **(3%)**

What other adverse events did the participants have?

A total of 66 participants who received at least 1 dose of trial drug had other adverse events. The table below shows the other adverse events that happened in at least half of all participants.

Other adverse events

	Part 1 Midostaurin 5 participants	Part 2 Midostaurin 30 participants	Part 2 Placebo 31 participants
Fever with low neutrophil count Febrile neutropenia	4 of 5 **(80%)**	25 of 30 **(83%)**	21 of 31 **(68%)**
Feeling sick to the stomach Nausea	5 of 5 **(100%)**	17 of 30 **(57%)**	17 of 31 **(55%)**
Diarrhea	2 of 5 **(40%)**	20 of 30 **(67%)**	17 of 31 **(55%)**
Fever Pyrexia	4 of 5 **(80%)**	13 of 30 **(43%)**	19 of 31 **(61%)**
Low red blood cell count Anaemia	3 of 5 **(60%)**	17 of 30 **(57%)**	15 of 31 **(48%)**
Platelet count decreased	1 of 5 **(20%)**	14 of 30 **(47%)**	18 of 31 **(58%)**

What was learned from this trial?

This trial helped researchers learn about the safety and effects of midostaurin in people with AML.

The researchers concluded that:

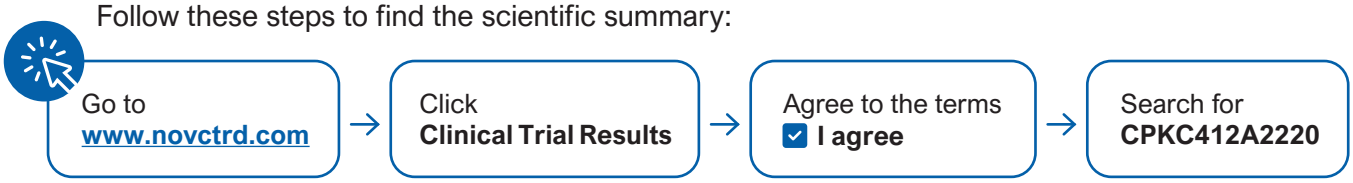
- They could not compare the event-free survival of the treatment groups due to a low number of participants.
- No new unexpected safety concerns were found.

Currently, there are no further studies with midostaurin planned.

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:

- clinicaltrials.gov – search using the number **NCT03280030**
- jrct.niph.go.jp/search – search using the number **jRCT2080223859**

If more trials are planned, they will appear on the public websites above. When there, search for midostaurin or acute myeloid leukemia.

Full clinical trial title: A Phase II, Randomized, Double-blind, Multi-center, Placebo-controlled Study to Evaluate the Efficacy and Safety of Twice Daily Oral Midostaurin in Combination With Daunorubicin/Cytarabine Induction, High-dose Cytarabine Consolidation, and Midostaurin Single Agent Continuation Therapy in Newly Diagnosed Patients With *FLT3*-mutated Acute Myeloid Leukemia (AML).

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