NOVARTIS

Clinical Trial Results Summary

A clinical trial to learn about the safety and effects of midostaurin in adults with acute myeloid leukemia (AML)

Protocol number: CPKC412A2408

Thank You!

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.

Thank you for taking part in this trial for the drug midostaurin, also known as PKC412. You helped researchers learn more about how midostaurin works in people with AML.

? **If you have any questions about the trial results, please talk to the doctor or staff at the trial site.**

How long was this trial?

This trial started in February 2018 and ended in July 2021. The entire duration, from enrolling the first participant to the last participant completing the trial, was around 3 years and 5 months. Each individual participant could have been in this trial for up to 1 year and 6 months.

Why was the research needed?

AML is cancer of the blood and the bone marrow. The bone marrow is found in the center of most bones, where new healthy blood cells are made. AML starts in the bone marrow and prevents it from making healthy blood cells. The cancer cells build up in the bone marrow and can also enter the blood stream and move to different parts of the body.

The main treatment for AML is chemotherapy. Chemotherapy uses medicines to kill cancer cells or stop them from growing and dividing. You can have chemotherapy through a drip into a vein, as a tablet you swallow or by an injection under the skin.

People with AML might have a procedure called a stem cell transplant. This procedure removes the cancerous cells from the bone marrow and replaces them with healthy cells taken, in most cases, from another healthy person, called a donor. The new cells can then multiply and produce healthy cells.

People with FLT3 positive AML have a mutation in the FLT3 gene. A mutation is a change in the structure of a gene. Midostaurin, when taken together with standard chemotherapy, is approved in the US and EU for the treatment of people with FLT3 positive AML.

Drug	***Pronounced as***
Midostaurin	MYE-doe-STAW-rin

In this study, researchers wanted to collect additional information on how safe and effective midostaurin is when used together with standard chemotherapy to treat adults with AML.

Who was in this trial?

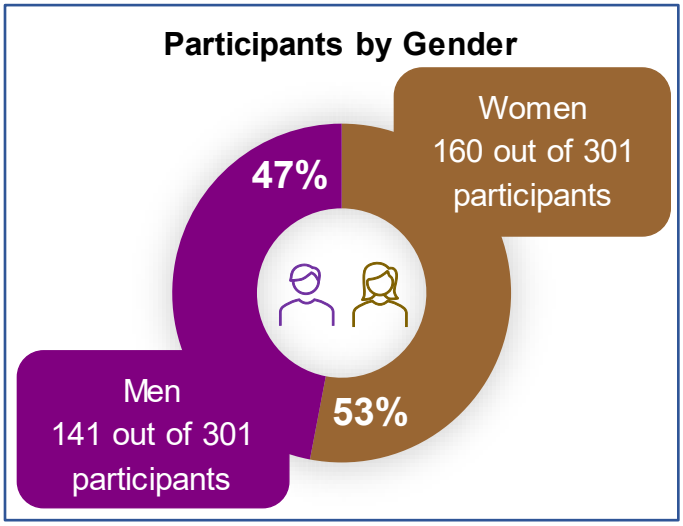
The participants could take part in this trial if they:

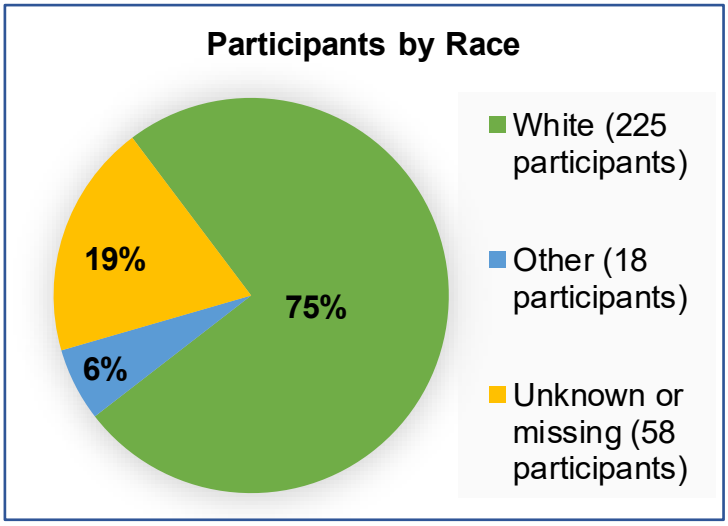
- were at least 18 years of age,
- were diagnosed with AML with FLT3 gene mutation,
- had started standard chemotherapy treatment, and
- were able to walk, capable of all self care and be out of bed for more than 50% of waking hours.

A total of 301 participants from 15 countries participated in this trial.

Number of participants in each country

Participants' age ranged from 19 to 85 years. The average age of participants was 56 years. Just over half of the participants were women (53%) and the majority of the participants were white (75%).





What treatments did the participants take?

Treatment drug		Standard chemotherapy treatments	
	**Midostaurin**, a drug used in treating adults with newly diagnosed AML. It is administered orally as 50 milligram (mg) capsules, twice a day.		**Cytarabine** was administered as an injection into the vein.
			**Daunorubicin or Idarubicin** was administered as an injection into the vein.

Drug	***Pronounced as***
Daunorubicin	DAW-noe-ROO-bi-SIN
Cytarabine	SYE-TAYR-a-been
Idarubicin	eye-DUH-RUE-bih-sin

What happened during this trial?

There were 3 treatment phases in this trial called Induction, Consolidation and Maintenance phase. All participants received the treatment in cycles during all 3 phases. Each cycle lasted for 28 days. Not all participants were able to complete all phases of the trial. This was because their cancer was not responding to treatment or because of medical problems.

301 participants

Induction phase: The aim of the induction phase was to clear AML from the participants' blood. Induction chemotherapy is also used as a first-line treatment for cancer to prepare the person for a stem cell transplant or other treatment. The participants who showed either CR⋆ or CRi⋆⋆ at the end of the induction phase could proceed to the consolidation phase.

⋆**Complete remission** (CR) - less than 5% (5 out of 100) of cells in the participant's bone marrow were cancer cells, with complete recovery of neutrophils* and platelets**. This means there were no signs of AML in the bone marrow or any part of the body, and the participant's blood cell count had recovered without the need of any blood transfusion.

⋆⋆**Complete remission with incomplete hematological recovery** (CRi) - less than 5% of cells in the participant's bone marrow were cancer cells, with incomplete recovery of neutrophils* and with or without complete recovery of platelets**. The participant may or may not have needed blood or platelet transfusion.

* *Neutrophils are a type of blood cells that fight infections.*

*** Platelets are a type of blood cells that helps to prevent or stop bleeding.*

- Participants took cytarabine for 7 (or 5) days and daunorubicin or idarubicin for 3 (or 2) days for 1 to 2 cycles (each cycle lasted 28 days).
- Participants also took 2 capsules of midostaurin 2 times a day from Day 8 to Day 28 for 1 to 2 cycles.

Up to 8 weeks

210 participants

Consolidation phase: The aim of the consolidation phase was to maintain the response the participant achieved at the end of the induction phase. Consolidation chemotherapy is administered after initial treatment, to target cancer cells that may still be present in the body. Participants could undergo stem cell transplant during the consolidation phase.

- Participants took cytarabine on Day 1, Day 3 and Day 5 for up to 4 cycles.
- Participants also took 2 capsules of midostaurin 2 times a day from Day 8 to Day 28 for up to 4 cycles.

Up to 16 weeks

93 participants

Maintenance phase: The aim of the maintenance phase was to maintain the response the participant achieved at the end of the last 2 phases.

- Participants continued taking 2 capsules of midostaurin 2 times a day from Day 1 to Day 28 for up to 12 cycles.
- Participants could continue taking the medicine as long as they benefitted from the treatment.
- Study doctors continued to monitor participants for 4 weeks after they stopped treatment.

Up to 48 weeks

What were the main results of this trial?

How many participants had medical problems during this trial?

Medical problems that happen in clinical trials are called “adverse events”.

An adverse event is an unwanted sign, symptom, or disease that participants have during a trial.

An adverse event is considered “serious” when it is life-threatening, causes lasting problems, or the participant needs hospital care. These problems may or may not be caused by the trial drug.

Category of adverse event	Number of participants (out of 301)	Percentage of participants
Any adverse event	295	98%
Adverse events that were severe but not life threatening and did not cause hospitalization	254	84%
Serious adverse events or serious medical problems	137	46%
Adverse events that led to discontinuation of the trial drug	40	13%
Adverse events that resulted in death	19	6%

What medical problems did the participants have during the trial?

A lot of research is needed to know whether a drug causes an adverse event. During a trial, all adverse events are recorded, whether or not they are thought to be caused by the trial drug. When new drugs are being studied, researchers keep track of all adverse events participants have.

This section is a summary of the adverse events that happened during this trial. The websites listed at the end of this summary may have more information about all the adverse events that happened in this trial.

How many participants had adverse events during induction, consolidation and maintenance phase?

	Midostaurin		
	Induction (Out of 301 participants)	**Consolidation** (Out of 210 participants)	**Maintenance** (Out of 93 participants)
At least 1 adverse event	285 (95%)	195 (93%)	58 (62%)
At least 1 serious adverse event	76 (25%)	67 (32%)	7 (8%)
Stopped drug due to adverse event	30 (10%)	9 (4%)	1 (1%)
Death	16 (5%)	3 (1%)	0

What were the most common serious adverse events?

The most common serious adverse events that happened in at least 2% (2 out of 100) of participants in any phase are shown below.

Number of Participants (%) With Most Common Serious Adverse Events

	Midostaurin		
Phases	**Induction** (Out of 301 participants)	**Consolidation** (Out of 210 participants)	**Maintenance** (Out of 93 participants)
Abnormally low neutrophil count with fever (Febrile neutropenia)	6 (2%)	26 (12%)	0
Body's extreme response to an infection (Sepsis)	4 (1%)	11 (5%)	0
Dangerously low blood pressure due to severe infection (Septic shock)	5 (2%)	6 (3%)	0
Inflammation in the large intestine. (Colitis)	5 (2%)	0	0
Insufficient oxygen in the lungs. (Respiratory failure)	5 (2%)	2 (1%)	0
Lung infection (Pneumonia)	9 (3%)	3 (1%)	1 (1%)
Lower than normal blood cell count (Cytopenia)	0	4(2%)	0

What were the most common non-serious adverse events?

The most common non-serious adverse events that happened in at least 20% (20 out of 100) of participants in any phase are presented below.

Number of Participants (%) With Most Common Non-Serious Adverse Events

	Midostaurin		
	Induction (Out of 301 participants)	**Consolidation** (Out of 210 participants)	**Maintenance** (Out of 93 participants)
Abnormally low number of neutrophils* accompanied with fever (Febrile neutropenia)	67 (23%)	44 (21%)	4(4%)
Constipation	32 (11%)	41 (20%)	2 (2%)
Decreased neutrophil count (Neutropenia)	33 (11%)	50 (24%)	12 (13%)
Diarrhea	97 (32%)	40 (19%)	8 (9%)
Feeling sick to the stomach (Nausea)	76 (25%)	67 (32%)	18 (19%)
Fever (Pyrexia)	93 (31%)	72 (34%)	3 (3%)
Headache	24 (8%)	47 (22%)	3 (3%)

** Neutrophils are a type of blood cell that fight infections.*

How many participants stopped trial drug due to adverse events?

During the trial, 40 out of 301 participants (13%) stopped midostaurin due to adverse events such as ***increase in liver test value of bilirubin** (blood bilirubin increased), ***increase in liver test value of alanine aminotransferase in the blood** (alanine aminotransferase increased), **inflammation in the large intestine** (colitis), **decreased neutrophil count** (neutropenia), **inflammation of the mouth and lips** (stomatitis).

**Increase in the liver test value of bilirubin and alanine aminotransferase indicates damage to the liver.*

What were the other results of this trial?

How many participants had complete remission (CR) or complete remission with incomplete hematologic recovery (CRi)?

301 participants were enrolled in this study and 300 of them received at least one dose of midostaurin. The results for these 300 participants are presented below.

Researchers found that:

- 196 out of 300 participants (65%) had CR
- 46 out of 300 participants (15%) had CRi

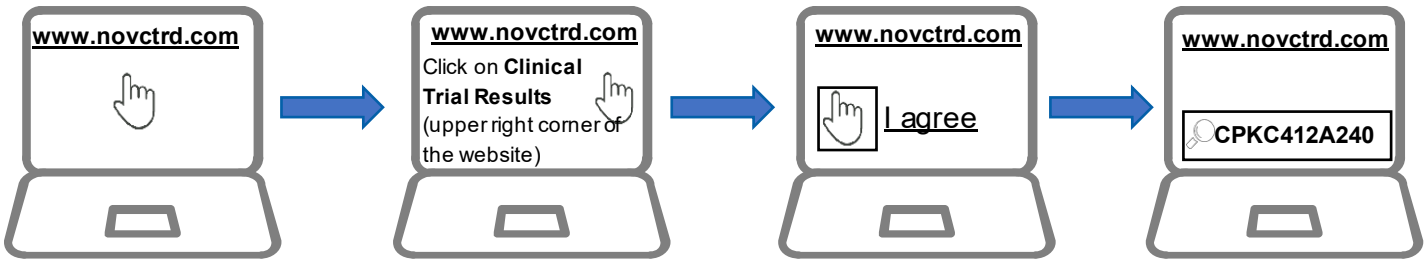
How was this trial useful?

This trial showed that the safety and effects of midostaurin with chemotherapy in participants with AML was similar to that shown in previous trials. Results from this trial may be used in other clinical trials for people with 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).

Please follow the below steps:



You can find more information about this trial on the following websites:

- www.clinicaltrials.gov Use the NCT identifier NCT03379727 in the search box.
- https://www.clinicaltrialsregister.eu/ctr-search/search Use the EudraCT identifier 2016-004440-12 in the search box.

Full clinical trial title: An open-label, multi-center, phase IIIb study to assess the safety and efficacy of midostaurin (PKC412) in patients 18 years of age or older with newly diagnosed FLT3-mutated acute myeloid leukemia who are eligible for "7+3" or "5+2" chemotherapy

Thank you

Thank you for taking part in this trial. As a clinical trial participant, you belong to a large community of people around the world. You helped researchers answer important health questions and test new medical treatments.

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

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