NOVARTIS

Clinical Trial Results Summary

A clinical trial to learn about the effects and safety of midostaurin with chemotherapy in people with newly diagnosed acute myeloid leukemia (AML) without an FLT3 gene mutation

Protocol number: CPKC412E2301

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 to the participants who took part in this trial for the drug midostaurin, also known as PKC412. You helped researchers learn more about how midostaurin works in people with newly diagnosed AML who did not have FLT3 gene mutation.

?

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

How long was this trial?

This trial started in July 2018 and ended in February 2021. The entire duration, from enrolling the first participant to the last participant completing the trial, was around 2 years and 7 months.

The sponsor ended this trial early because the initial results of the trial suggested that midostaurin did not show a beneficial effect in participants with newly diagnosed AML who did not have FLT3 mutations. People who have AML may have certain changes in the gene, known as gene alterations or mutations. People with FLT3 positive AML have a mutation in the FLT3 gene. When the trial ended, researchers created a report of the trial results. This summary is based on that report.

Why was the research needed?

Researchers were looking for a better way to treat people with newly diagnosed AML and no mutation in the FLT3 gene.

AML is cancer of the blood and the bone marrow. 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. Chemotherapy can be given through an intravenous drip into a vein, or as a tablet to be swallowed, 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.

Midostaurin is approved for use in combination with standard chemotherapy treatments such as cytarabine and daunorubicin/idarubicin induction and cytarabine consolidation chemotherapy for treating people with FLT3 positive AML.

Drug	***Pronounced as***
Midostaurin	mye-doe-STAW-rin
Daunorubicin	daw-no-ROO-bi-sin
Cytarabine	sye-TA-ra-been
Idarubicin	eye-duh-RUE-bi-sin

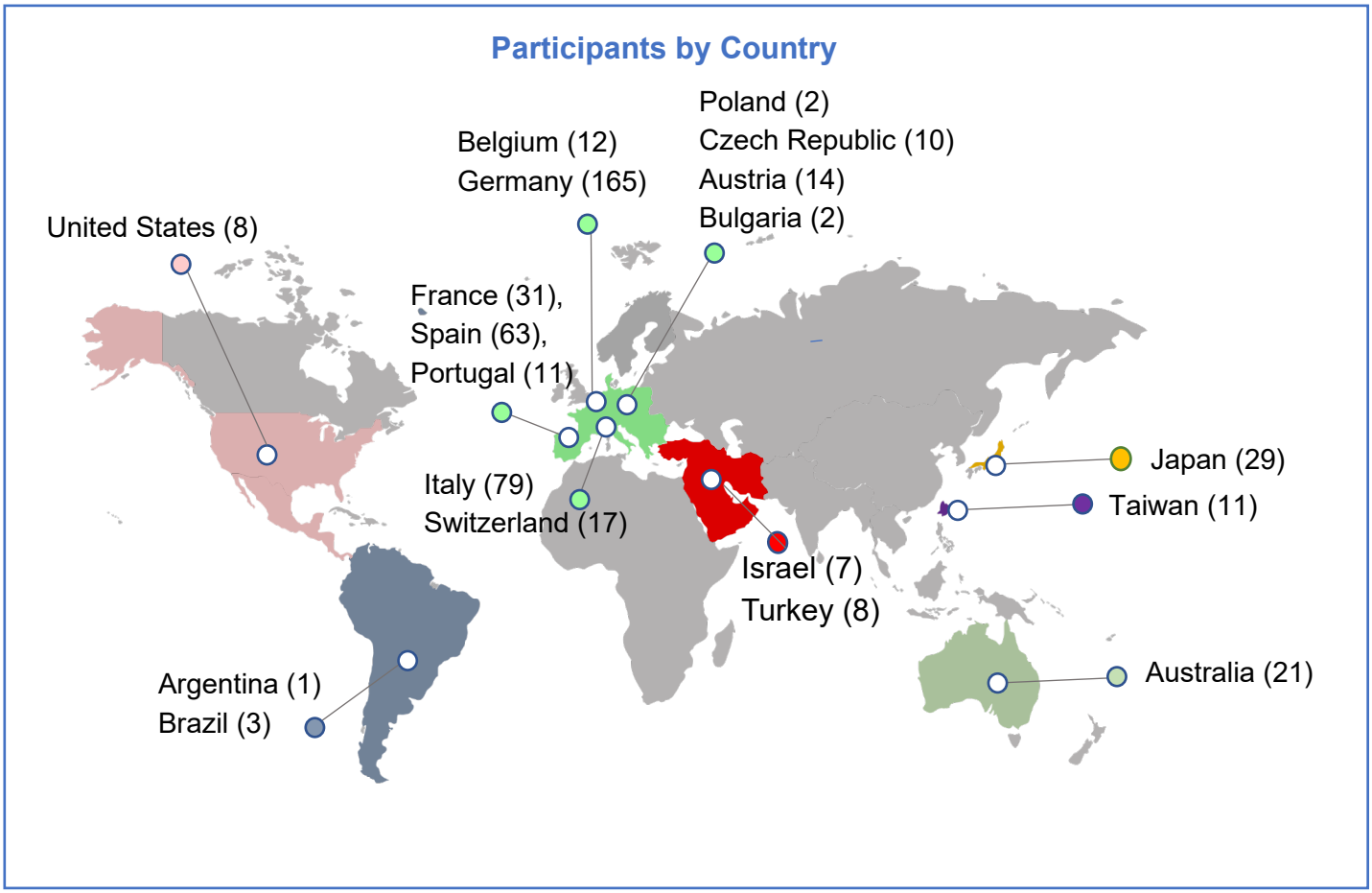
In this trial, researchers wanted to check if midostaurin works in people who were newly diagnosed with AML and did not have a mutation in the FLT3 gene.

Who was in this trial?

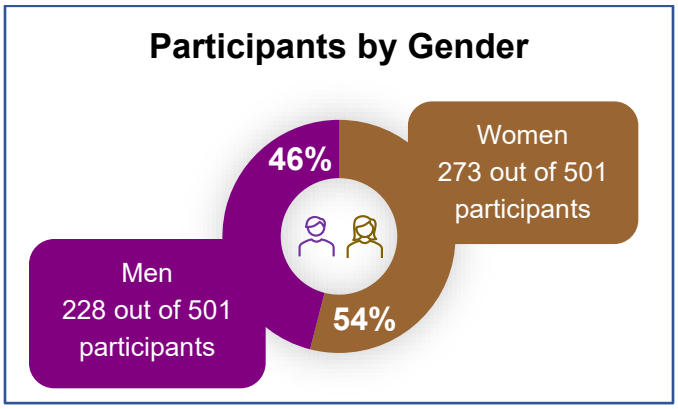
The participants could take part in this trial if they:

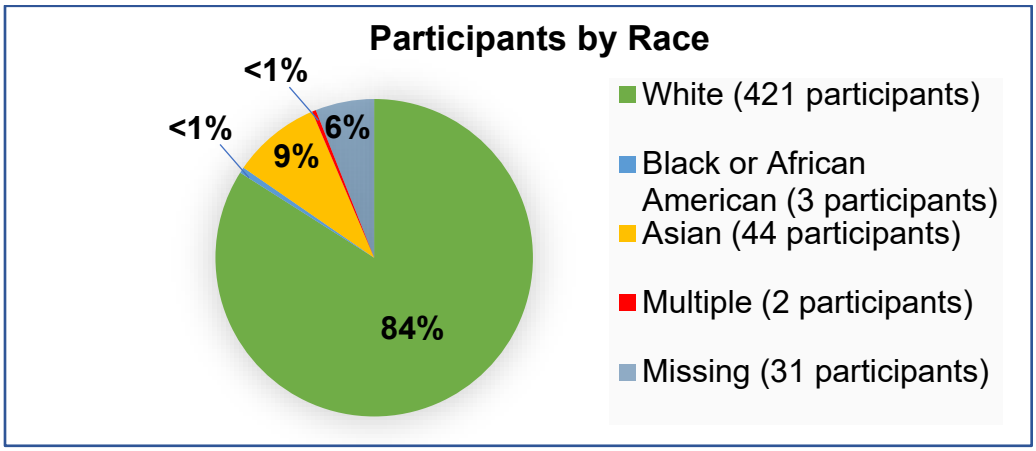
- had newly diagnosed acute myeloid leukemia (AML) and did not have FLT3 gene mutations as confirmed by a validated laboratory test
- were at least 18 years of age
- did not have any other diseases
- could undergo thorough chemotherapy

A total of 501 participants from 20 countries were randomly assigned to midostaurin or to placebo treatment groups using a computer system to make sure the groups were distributed fairly.
494 participants actually received treatment.



The average age of participants was 56 years. Participants' ages ranged from 18 to 79 years.





What treatments did the participants take?

The drugs given in this trial were:

Study treatments		Standard chemotherapy treatments	
	**Midostaurin**, a drug that was tested in participants who were newly diagnosed with AML and did not have the FLT3 gene mutation. It was administered as capsules (50 milligrams [mg] two times a day)		**Cytarabine** (chemotherapy) was administered into the vein.
	**Placebo**, which looked like the trial drug, but did not have any medicine in it. Using a placebo helps researchers better understand the effect of a trial drug by making sure that the changes were not happening by chance.		**Daunorubicin or Idarubicin** (chemotherapy) was administered into the vein.

What happened during the trial?

Before Treatment (2 weeks)

The trial doctors checked if participants could take part in this trial based on their FLT3 mutation status and were otherwise eligible for the trial.

None of the participants, trial doctors, or trial staff knew what treatment participants were receiving.

During Treatment (1 cycle is 28 days)

There were four treatment phases called Induction 1, Induction 2, Consolidation, and Post Consolidation phase.

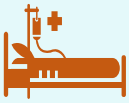
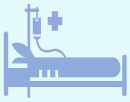
Induction Phase: Induction chemotherapy is used as a first-line treatment for cancer to prepare the person for a stem cell transplant or other treatment. Participants who achieved complete remission (CR) after Induction 1 entered the consolidation treatment phase, otherwise they received Induction 2. All participants received at least one cycle of induction therapy (initial treatment) with cytarabine and daunorubicin or idarubicin.

Complete remission meant less than 5% of cells in the participant's bone marrow were cancer cells, with complete recovery of neutrophils and platelets (there were no signs of AML in the bone marrow or any part of the body, and the participant's blood cells had recovered without the need of any transfusion, providing blood). Neutrophils are a type of white blood cells that fight bacteria. Platelets are a type of blood cells that helps in preventing/stopping bleeding.

Consolidation Phase: Consolidation chemotherapy is administered after initial treatment to target cancer cells that may still be in the person's body.

Participants could undergo stem cell transplant during the consolidation phase.

Post Consolidation Phase: The participants received only midostaurin during this phase for 12 cycles to make sure that cancer cells won't come back.

Treatment Phases 1 cycle = 28 days		**and**			**or**	
Treatment Phases 1 cycle = 28 days	Day 1-3 Daunorubicin/ Idarubicin		Day 1-7 Cytarabine	From Day 8 (until 48 hours before start of the next cycle) Midostaurin (250 participants) or Placebo (251 participants)		
Induction 2* (1 cycle)	Day 1-3 Daunorubicin/ Idarubicin		Day 1-3 Cytarabine	From Day 4 (until 48 hours before start of the next cycle) Midostaurin or Placebo		
Consolidation (3-4 cycles)				From Day 4 (until 48 hours before start of the next cycle) Midostaurin or Placebo		
Post-consolidation (12 cycles)	Days 1-28 Midostaurin					

**For participants who did not achieve CR after induction 1*

After Treatment (every 12 weeks)

The participants' health was monitored during this period. No drug was given during the follow up period. However, participants could go on to receive other anti-cancer therapy.

What were the main results of this trial?

The main question the researchers wanted to answer in this trial was:

Did participants have more time without an event* when treated with midostaurin with chemotherapy compared to placebo with chemotherapy?

* An event is when the participant's AML did not respond to treatment; their AML came back; or they died of any cause

To answer this question, researchers measured the time between treatment and having a specific event. The time between randomization and having a specific event was around 6 months for both the midostaurin with chemotherapy and the placebo with chemotherapy groups. Therefore, the trial treatment did not show a beneficial effect in participants with newly diagnosed AML who had no FLT3 mutations.

What medical problems did the participants have during the trial?

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

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.

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.

How many participants had adverse events?

The adverse events that happened in the 2 treatment groups during the trial are listed in the table below.

Number of Participants (%) With Adverse Events

Category / Groups	**Midostaurin + chemotherapy** (out of **245**)	**Placebo + chemotherapy** (out of **249**)
At least 1 adverse event	244 (99.6%)	247 (99%)
At least 1 serious adverse event	95 (39%)	114 (46%)
Stopped drug due to adverse event	43 (18%)	33 (13%)
Deaths	46 (19%)	53 (21%)

What were the most common serious adverse events?

The most common serious adverse events that happened in at least 5% (5 out of 100) of participants in any group are shown below:

Events / Groups	**Midostaurin + chemotherapy** (Out of **245**)	**Placebo + chemotherapy** (Out of **249**)
Abnormally low number of neutrophils accompanied with fever (Febrile neutropenia)	16 (7%)	23 (9%)
Body's extreme response to an infection (Sepsis)	11 (5%)	13 (5%)
Lung infection (Pneumonia)	9 (4%)	12 (5%)

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 group are presented below.

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

Events / Groups	**Midostaurin + chemotherapy** (out of **245**)	**Placebo + chemotherapy** (out of **249**)
Abnormally low number of neutrophils[a] **accompanied with fever** (Febrile neutropenia)	102 (42%)	116 (47%)
Abnormally low blood platelet[b] **count** (Thrombocytopenia)	62 (25%)	69 (28%)
Vomiting (Vomiting)	101 (41%)	63 (25%)
Constipation (Constipation)	77 (31%)	84 (34%)
Decreased neutrophil count (Neutropenia)	34 (14%)	53 (21%)
Decrease of red blood cells in the blood (Anaemia)	77 (31%)	96 (39%)
Diarrhoea (Diarrhoea)	121 (49%)	142 (57%)
Feeling sick to the stomach (Nausea)	141 (58%)	137 (55%)
Fever (Pyrexia)	146 (60%)	138 (55%)
Headache (Headache)	70 (29%)	64 (26%)
Inflammation of the inner lining of the body and its organs (Mucosal inflammation)	47 (19%)	50 (20%)
Low levels of potassium in blood (Hypokalaemia)	95 (39%)	102 (41%)
Low blood platelet count (Platelet count decreased)	34 (14%)	50 (20%)
Rash (Rash)	80 (33%)	87 (35%)

[a] Neutrophils are a type of white blood cells that fight bacteria.

[b] Platelets are a type of blood cells that helps in preventing/stopping bleeding.

How many participants stopped trial drug due to adverse events?

During the trial, 43 out of 494 (18%) of participants stopped midostaurin early due to adverse events such as infection causing organ failure and dangerously low blood pressure (Septic shock), feeling sick to the stomach (Nausea) and being sick (Vomiting).

How was this trial useful?

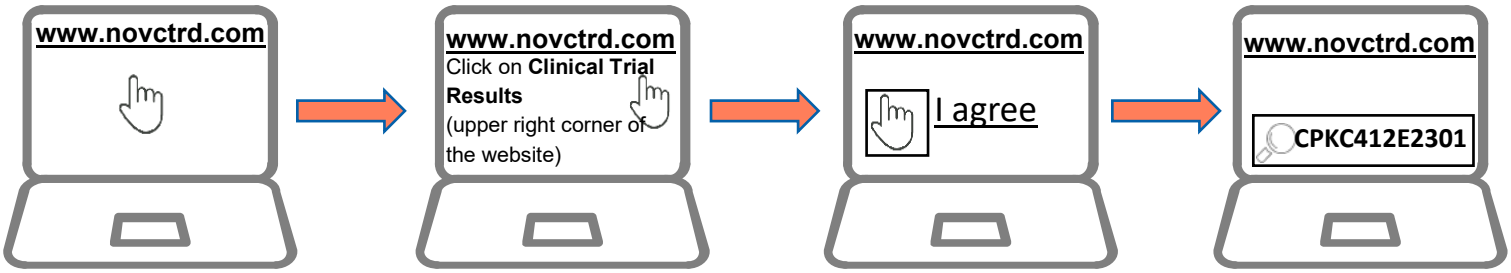
The trial helped researchers to learn about the safety and effects of midostaurin in participants with newly diagnosed AML without FLT3 mutations. The trial ended early as the initial analysis suggested that midostaurin + standard chemotherapy was not effective in treating patients with newly diagnosed AML without FLT3 mutation.

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

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 NCT03512197 in the search box.
- https://www.clinicaltrialsregister.eu/ctr-search/search Use the EudraCT identifier 2017-003540-21 in the search box.

Full clinical trial title: A phase III, randomized, double-blind study of chemotherapy with daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation plus midostaurin (PKC412) or chemotherapy plus placebo in newly diagnosed subjects with *FLT3* mutation negative acute myeloid leukemia (AML)

Thank you

Thank you to all trial participants. Clinical trial participants belong to a large community of people who take part in clinical research around the world. They help researchers answer important health questions and test new medical treatments for patients.

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