



Daiichi-Sankyo

Clinical Results Summary

A clinical study to learn about the safety and effects of PLX3397 in people with a type of returning or treatment-resistant blood cancer called acute myeloid leukemia

Protocol number: PLX108-05

Thank You!



Daiichi Sankyo, Inc., the sponsor of this study, would like to thank the participants who took part in this study for PLX3397. Each participant helped to advance medical research for people affected with a type of blood cancer called acute myeloid leukemia. Their contribution to medicine and healthcare is greatly appreciated.

Important note: This summary only shows the results of a single study. Other studies may have different findings. Researchers and health authorities look at the results of many studies to understand which treatments work and how they work. It takes a lot of people in many studies around the world to advance medical science and healthcare.

Do not use the results of this study to make health decisions. Please talk to a doctor before changing any treatment you are taking or if you have any questions about these study results.

What was the main purpose of this study?

Returning or treatment-resistant FLT3-ITD positive AML

Researchers were looking for a better way to treat people with a type of blood cancer called acute myeloid leukemia, or AML. The participants in this study had AML that either:

- responded to treatment, but their cancer returned within 6 months (known as relapsed AML), or
- did not respond to first treatment (known as refractory AML).

AML is a type of 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 normal blood cells. The abnormal (cancer) cells build up in the bone marrow and can also enter the blood stream and move to different parts of the body.

The most common treatment for AML is chemotherapy. Chemotherapy uses medicine to kill cancer cells or stop them from growing and dividing. People with AML might also have a procedure called a stem cell transplant, which removes the cancerous cells from the bone marrow and replaces them with healthy cells from another healthy person (donor). The new cells can then multiply and produce more healthy cells.

People who have AML may have certain gene alterations (or mutations). People with FLT3-ITD positive AML have an alteration in the FLT3 gene. FLT3-ITD positive AML is often severe, does not respond well to standard treatment, and is likely to come back even after treatment. PLX3397, the study treatment, is a drug designed to work against AML cancer cells by stopping the activity of this gene mutation.

Treatment given in this study



PLX3397

An investigational treatment being studied for the treatment of relapsed or refractory acute myeloid leukemia in participants who have an FLT3-ITD gene mutation. When the study started, PLX3397 was not approved for use. This means that it could only be used in a research study such as this one.

Main goal of this study

The main question researchers wanted to answer in this study was:



How many participants showed either a complete response to treatment with PLX3397 or discontinued treatment to have a stem cell transplant?

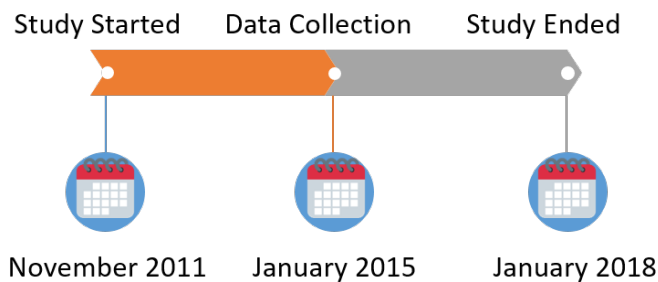
Other goals of this study

Researchers also wanted to answer the following questions:

- How many participants had at least 50% reduction in AML after treatment?
- What were the participants condition and life duration after initial response to PLX3397 treatment?

Researchers also closely monitored the health of the participants throughout the study.

How long was this study?



The study was designed so that participants could continue in it as long as their cancer did not get worse and they did not have serious side effects. The study started in November 2011 and ended in January 2018.

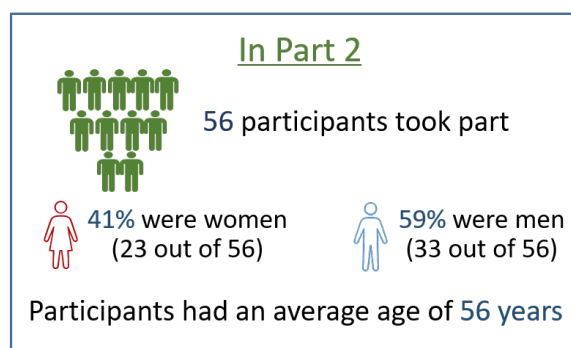
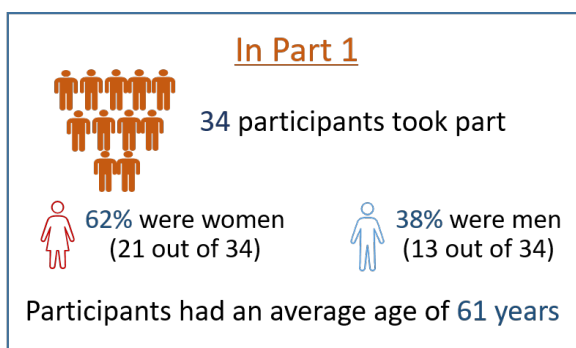
The results were collected up to January 2015 and a study report was created. This summary is based on that report. The study ended as planned in January 2018.

Who was in this study?

This study included 90 participants from the United States.

Men and women could take part in this study if they:

- were 18 years of age or older,
- either did not respond to their first treatment for AML, their cancer returned within 6 months of receiving treatment, or they had been newly diagnosed with FLT3-ITD positive AML and standard treatment could not be used,
- tested positive for the FLT3-ITD mutation at the time of entering into the study,
- agreed to a bone marrow analysis to enter into Part 2,
- had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2, meaning they were either fully active, unable to do hard physical activity but able to walk and do light work, or unable to work but able to walk and manage selfcare, and
- had adequate liver and kidney function.



What happened during this study?

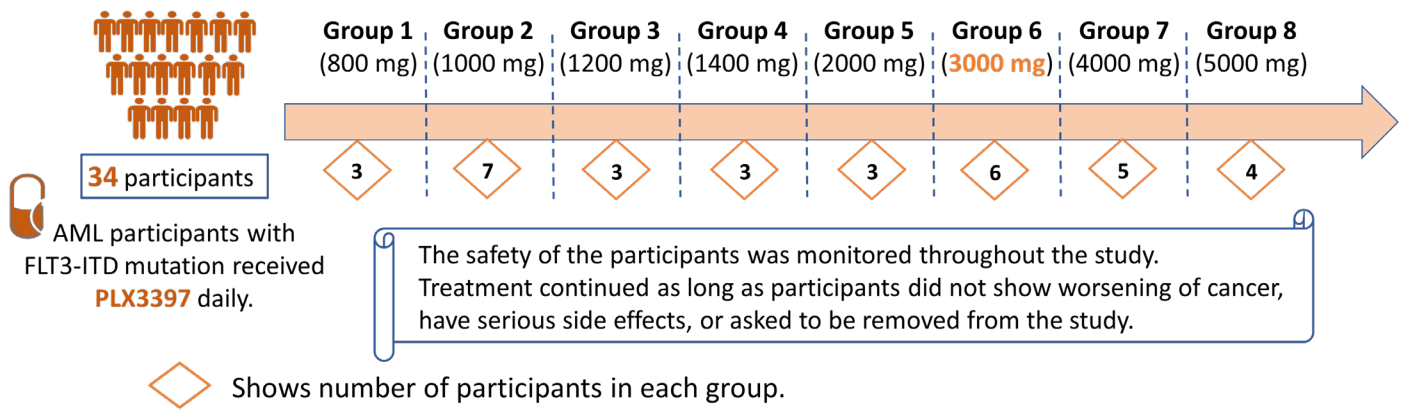
This was a Phase 1/2 study that was divided into 2 parts. Part 1 was a Phase 1 study, which are sometimes done to find the highest dose of a drug that can be safely given to participants. Part 2 was a Phase 2 study done to better understand if a drug can treat the condition it has been developed for.

This study was also “open label”. This means that both the researchers and the participants knew which treatment was given to which participants. Participants first completed a screening period to find out if they could take part in the study. 90 participants who passed screening were assigned to 2 groups: 34 participants in Part 1 and 56 participants in Part 2.

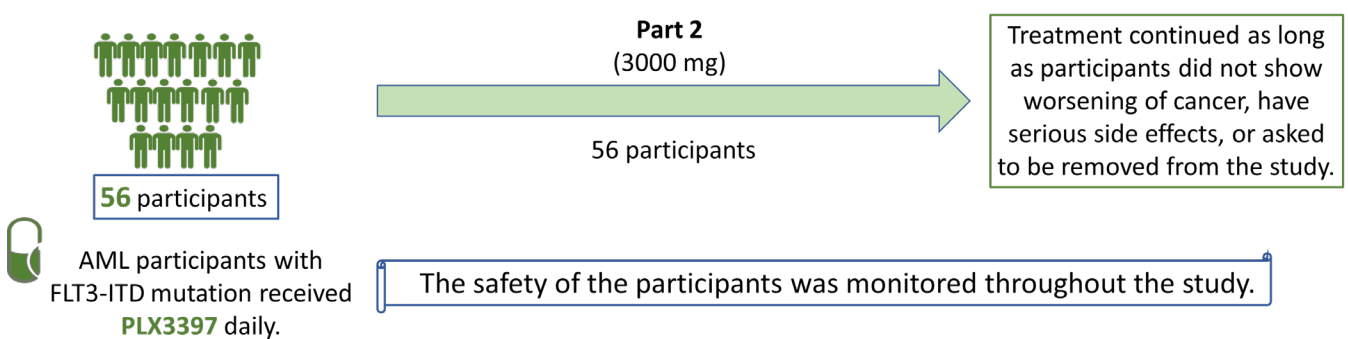
In **Part 1**, researchers started by giving 800 milligrams (mg) of PLX3397 to the participants in Group 1. If this dose was considered to be safe by the researchers, the next group of participants received a higher dose of PLX3397. This process was repeated with increasingly higher doses, as shown in the study design figure below, until the highest dose that could safely be given was identified. For all groups, PLX3397 was given by mouth twice daily for a total of the dose being studied for that group. The researchers identified 3000 mg as the highest dose of PLX3397 in Part 1 that could safely be given to participants.

In **Part 2**, this dose of 3000 mg PLX3397 was given to all participants to learn about their response to treatment. The participants in both parts continued to receive treatment as long as they did not show worsening of cancer, have serious side effects, or asked to be removed from the study.

Study Design – Part 1



Study Design – Part 2



What were the key results of this study?

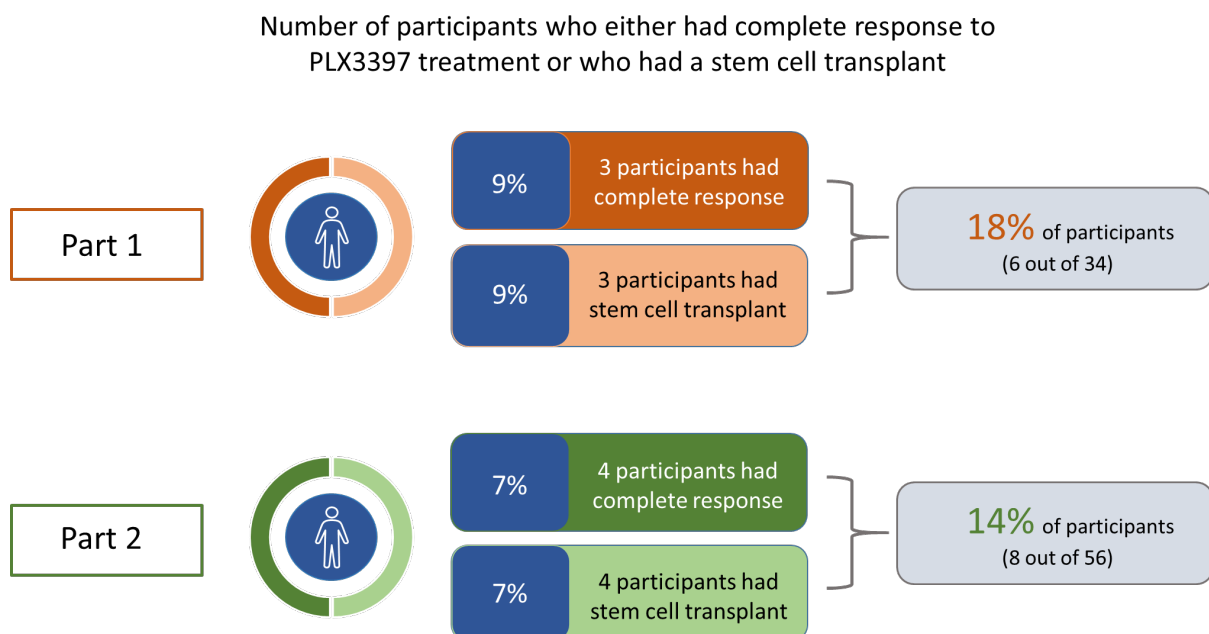
Key results from this study are shown for the total group of participants as average results. This summary does not show the results from each individual participant. An individual participants' results could be different from the total group of participants. A full list of the questions the researchers wanted to answer and a detailed presentation of the results can be found on the website listed at the end of this summary.

How many participants showed either a complete response to treatment with PLX3397 or discontinued treatment to have a stem cell transplant?

To answer this question, researchers recorded the total number of participants who either:

- showed a complete response to treatment, meaning they had
 - complete disappearance of AML with complete recovery of neutrophil count, or
 - complete disappearance of AML, with or without complete recovery of neutrophil count or platelet count
- had a stem cell transplant procedure and therefore discontinued study treatment

Neutrophils are a type of white blood cells that help fight infections. Platelets are a type of blood cells that help prevent/stop bleeding.



What were the other results of this study?

How many participants had at least 50% reduction in AML after treatment?

In addition to the participants who showed complete response, an additional **12%** (4 out of 34) of participants in Part 1 and **9%** (5 out of 56) of participants in Part 2 had at least 50% reduction in AML after treatment.

What were the participants' condition and life duration after initial response to PLX3397 treatment?

Researchers further monitored participants who either had a complete response to treatment or at least 50% reduction in AML and measured how long it took for AML to return or get worse. Researchers also recorded the length of time participants lived since they started treatment with PLX3397.

The results presented below show the amount of time it took about half of the participants to reach each of the timepoints. This means that for half of the participants, it took less time and for the other half of participants, it took more time.

For participants who had 50% reduction in AML or a better response, how long did they live until their cancer got worse or they died?

Part 1
11 weeks

Part 2
13 weeks

For participants who had complete response to treatment, how long did they live until their cancer came back or they died?

Part 1
26 weeks

Part 2
41 weeks

How long did participants live until their cancer got worse or they died after initiating treatment with PLX3397?

Part 1
8 weeks

Part 2
7 weeks

How long did participants live after initiating treatment with PLX3397?

Part 1
13 weeks

Part 2
16 weeks

What medical problems did the study participants have?

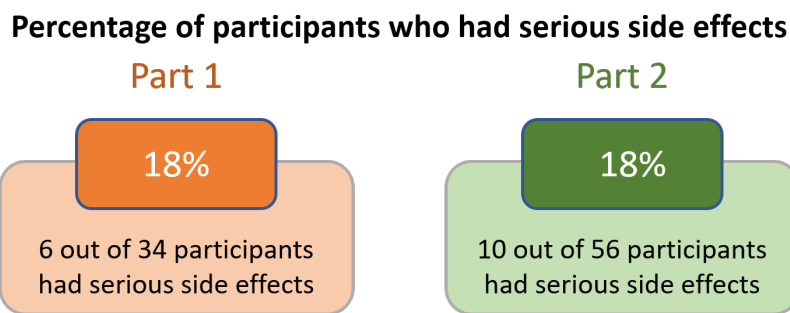
Side effects are medical problems (such as feeling tired) that happened during the study which the study doctor thought could be related to the treatments in the study. This section provides a summary of side

effects related to the study treatment PLX3397. The website listed at the end of this summary has more information about the medical problems that happened in this study.

Side effects are considered serious if they cause death, are life-threatening, cause lasting problems, or require hospitalization. Some participants stop study treatment because of side effects.

How many participants had serious side effects?

In this study, serious side effects were monitored for 34 participants in Part 1 and 56 participants in Part 2 who took PLX3397.



In both Part 1 and Part 2, the most frequently reported serious side effect was of abnormally low number of neutrophils accompanied with fever. Neutrophils are a type of white blood cells that help fight infections. Other common serious side effects reported by participants are presented below.

Part 1

- Inflammation of the digestive tract caused by infections
- Inflammation of the inner lining of the body and its organs
- Itchy and painful rashes all over the body
- Lung infection

Part 2

- High blood pressure
- Inflammation of the digestive tract
- Loss of fluid from the body
- Lung infection caused by fungus
- Painful skin lesions accompanied with fever and swollen joints
- Purple-colored spots on the skin
- Rash with raised red bumps on the skin

Number of deaths

There was 1 death during Part 2 due to a side effect of fever combined with multiple organ failure.

What were the most common side effects?

The most common side effects, both serious and non-serious, reported by at least 15% (15 out of 100) of participants in any group are reported below.

Most common side effects in Part 1

Group Dose # of participants	Group 1 800 mg (Out of 3)	Group 2 1000 mg (Out of 7)	Group 3 1200 mg (Out of 3)	Group 4 1400 mg (Out of 3)	Group 5 2000 mg (Out of 3)	Group 6 3000 mg (Out of 6)	Group 7 4000 mg (Out of 5)	Group 8 5000 mg (Out of 4)
Change in taste	0	1 (14%)	0	2 (67%)	2 (67%)	2 (33%)	0	2 (50%)
Decrease in appetite	1 (33%)	0	0	1 (33%)	1 (33%)	2 (33%)	1 (20%)	1 (25%)
Diarrhea	1 (33%)	1 (14%)	1 (33%)	1 (33%)	1 (33%)	0	3 (60%)	1 (25%)
Feeling sick to stomach	2 (67%)	1 (14%)	2 (67%)	3 (100%)	0	2 (33%)	1 (20%)	3 (75%)
Feeling tired	0	1 (14%)	1 (33%)	1 (33%)	1 (33%)	2 (33%)	1 (20%)	2 (50%)
Increase in liver test value of aspartate amino transferase in the blood	0	0	0	0	1 (33%)	1 (17%)	1 (20%)	1 (25%)
Low hemoglobin levels in the blood	0	1 (14%)	1 (33%)	1 (33%)	0	0	0	2 (50%)
Vomiting	0	2 (29%)	1 (33%)	2 (67%)	0	2 (33%)	1 (20%)	3 (75%)

Most common side effects in Part 2

Side effect	Number of participants (Out of 56) 3000 mg	Side effect	Number of participants (Out of 56) 3000 mg
Change in taste	6 (11%)	Feeling tired	18 (32%)
Decrease in appetite	16 (29%)	Increase in liver test value of aspartate aminotransferase in the blood	10 (18%)
Diarrhea	19 (34%)	Low hemoglobin levels in the blood	9 (16%)
Feeling sick to stomach	21 (38%)	Vomiting	15 (27%)

How many participants had to stop treatment because of side effects?

In Part 1, **2** participants stopped treatment due to abnormally low number of neutrophils accompanied with fever. Neutrophils are a type of white blood cells that help fight infections.

In Part 2, **2** participants stopped treatment, one due to abnormally low number of neutrophils accompanied with fever and the other due to a rash with raised red bumps on the skin.


How was this study useful for patients and researchers?

This study helped researchers learn about how participants with returning or treatment-resistant AML positive for FLT3-ITD mutation respond to PLX3397 treatment. Findings from this study may be used to seek approval to use study treatment in patients with AML who have an FLT3-ITD mutation. Other studies for PLX3397 are ongoing.

Please remember, this summary only shows the results of a single study. Other studies may have different findings. Please talk to a doctor before changing any treatment you are taking or if you have any questions about these study results.

Where can I learn more about this study?

You can find more information about this study on the following website:

 www.clinicaltrials.gov: Use the NCT identifier NCT01349049 in the search field.

Please remember that the results on this website may be presented in a different way. If you were a study participant and have questions about the results of this study, please speak with the doctor or staff at your study site.

Full study title: A Phase 1/2 Safety and Efficacy Study of Orally Administered PLX3397 in Adults With Relapsed or Refractory Flt3-ITD-positive Acute Myeloid Leukemia

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Date of this summary: 02 October 2020

This summary was prepared by Kinapse Ltd, a Syneos Health® company.