



Daiichi-Sankyo

Clinical Results Summary

A clinical study to understand the effects of Pexidartinib on liver enzymes CYP3A4 and CYP2C9 in people with cancer

Protocol number: PL3397-A-U126

Thank You!



Daiichi Sankyo, Inc., the sponsor of this study, would like to thank the participants who took part in this study for pexidartinib also known as PLX3397. Each participant helped to advance medical research for people affected with cancer. 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?

Pexidartinib, the study drug being tested, stops the growth of tumor cells by preventing the protein 'kinase' from working.

Earlier studies have shown that pexidartinib could stop the action of certain liver enzymes. Liver enzymes CYP3A4 and CYP2C9 are responsible for breaking down several drugs into active and inactive products in the body. In this study, researchers wanted to learn how pexidartinib affects the blood levels of drugs broken down by these enzymes. They chose to study the levels of drugs midazolam and tolbutamide. CYP3A4 breaks down midazolam and CYP2C9 breaks down tolbutamide.

Researchers also wanted to understand the effects and safety of pexidartinib for treating various tumours.

Treatments given in this study

The treatments given in this study were

Pexidartinib (Study drug)

Drug being studied for the treatment of tumors. When the study started, pexidartinib was not approved for use. This means that it could only be used in a research study such as this one.

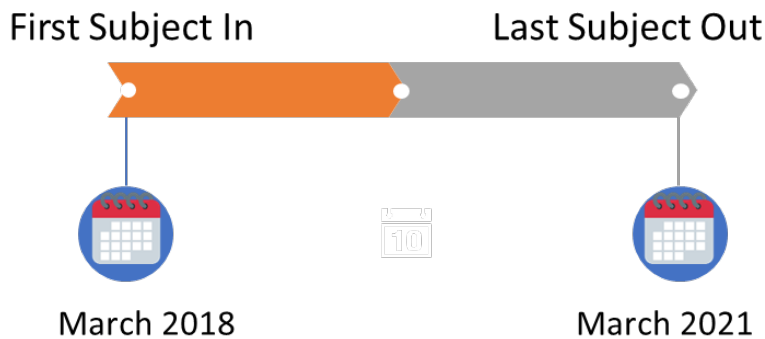
Main goals of this study

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

What was the effect of pexidartinib on the blood levels of midazolam and tolbutamide in participants?



How long was this study?



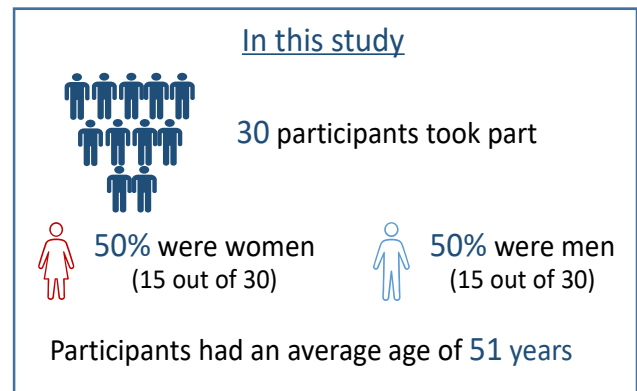
This summary is based on that report.

Who was in this study?

This study included 30 participants from the United States, the Netherlands, New Zealand, and Taiwan.

Participants could take part in this study if they:

- were 18 years and above,
- had tumor growth in or around the joint due to tenosynovial giant cell tumor (TGCT), skin cancer, stomach cancer, or other solid tumors for which there was no standard treatment, and
- had normal blood, liver, and kidney function that were within the range specified for the study.



What happened during this study?

This was a Phase 1 study. Phase 1 studies are done to find out how a new study drug works in a small number of participants. This helps researchers understand what happens to the study drug in the body, and if there are any side effects. This study was also “open label”. This means that both the researchers and the participants knew which treatment was given to participants.

Participants first completed a screening period to find out if they could take part in the study.

This study was done in 2 parts:

Part 1

Part 1 of the study was done to understand how pexidartinib affects midazolam and tolbutamide in the body. A total of 30 participants were treated in Part 1 of this study.

On Day 1, participants received a single dose of 2 milligrams (mg) of midazolam and 500 mg tolbutamide.

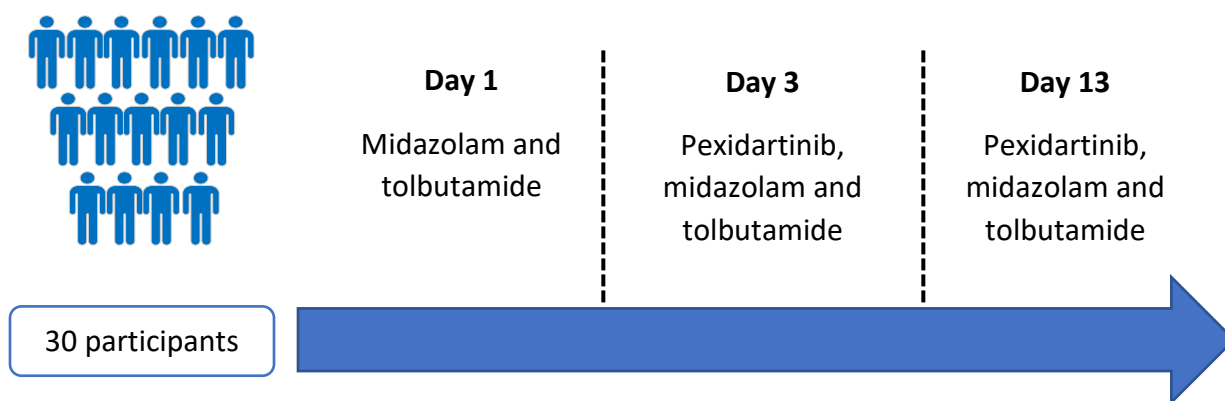
Starting from Day 3, participants received 400 mg of pexidartinib capsules twice a day until Day 15. On the morning of Day 3, participants also received a single dose of midazolam (2 mg) and tolbutamide (500 mg).

On Day 13, participants received the same doses of pexidartinib, midazolam, and tolbutamide as Day 3.

Researchers collected blood samples from participants at regular intervals on Day 1, Day 3, and Day 13 and measured the blood levels of all the drugs.

What happened in this study

Part 1

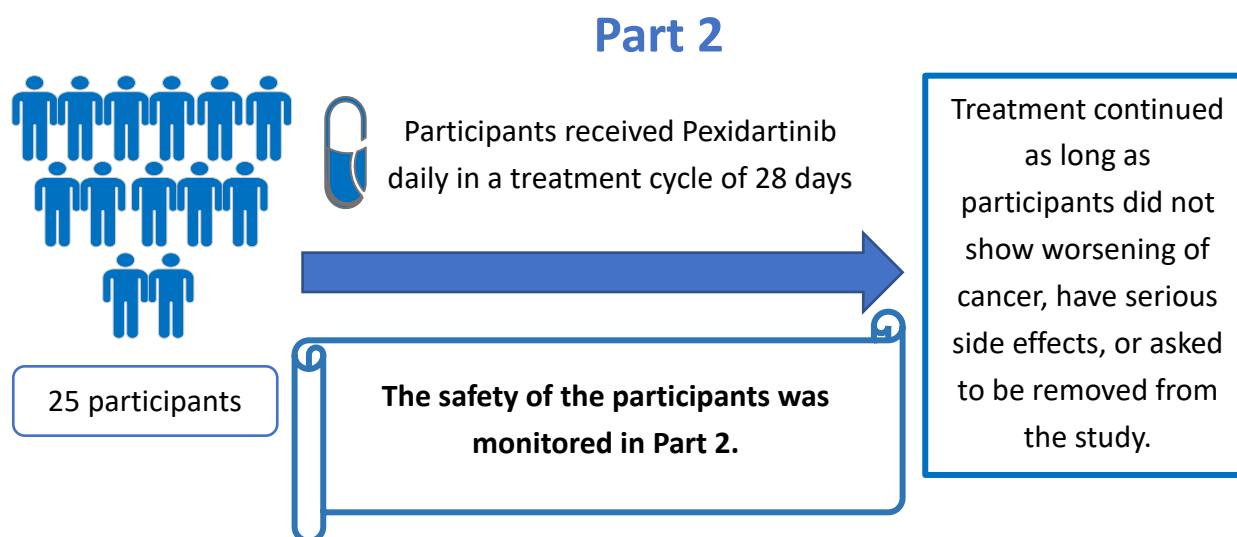


Part 2

Participants who completed treatment during Part 1, entered Part 2 of the study. In Part 2, 25 participants continued to receive pexidartinib 800 mg daily, for as long as they benefited from the treatment without any serious side effects.

The researchers used magnetic resonance imaging (MRI), and computed tomography (CT) scan to check the participants' tumor size. They closely monitored the health of the participants.

What happened in this study



All participants in Part 2 discontinued the study.

What was the key result 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 participant's 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 websites listed at the end of this summary.

What was the effect of pexidartinib on the blood levels of midazolam and tolbutamide in participants?

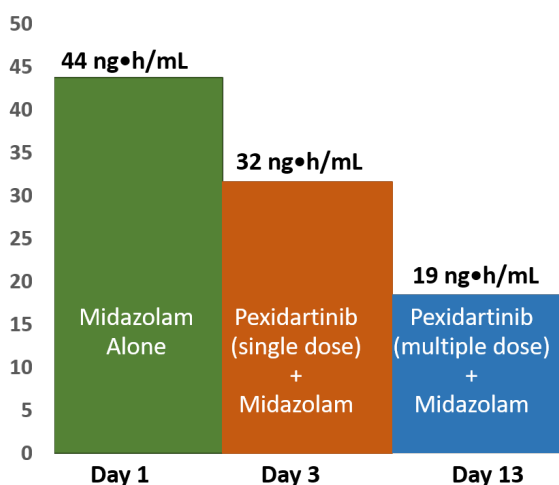
Compared to when midazolam was given alone on Day 1, the blood levels of midazolam decreased by **21%** after a single dose of pexidartinib on Day 3. By Day 13, the blood levels of midazolam decreased by **52%** after multiple doses of pexidartinib. This means that pexidartinib increased the rate at which CYP3A4 worked and broke down midazolam.

Compared to when tolbutamide was given alone on Day 1, the blood levels of tolbutamide increased by **15%** after a single dose of pexidartinib on Day 3. By Day 13, the blood levels of tolbutamide increased by **36%** after multiple doses of pexidartinib. This means that pexidartinib reduced the rate at which CYP2C9 worked and broke down tolbutamide.

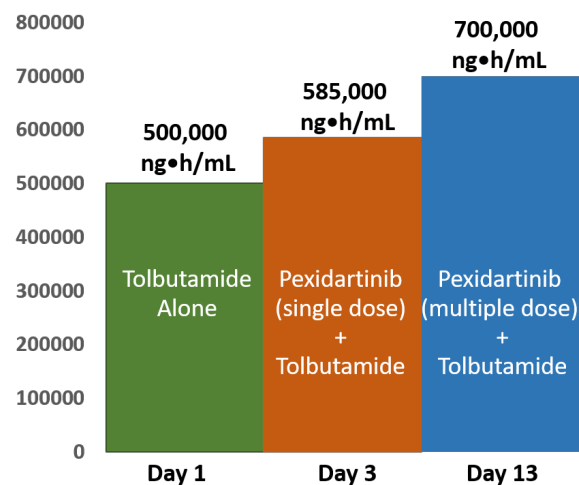
How was this measured?

Researchers collected blood samples and measured the total levels of midazolam and tolbutamide in participants' blood on Day 1, Day 3, and Day 13 in units, nanograms hours per milliliter (ng•h/mL). This shows how much midazolam and tolbutamide in nanograms (one thousand-millionth of a gram) was found in each milliliter of blood over time.

Total levels of Midazolam in participants' blood



Total levels of Tolbutamide in participants' blood



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 doctors thought could be related to the treatments in the study. This section provides a summary of side effects related to pexidartinib. The websites listed at the end of this summary have 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 related to pexidartinib?

Serious side effects reported by participants in both Part 1 and Part 2 are presented below:

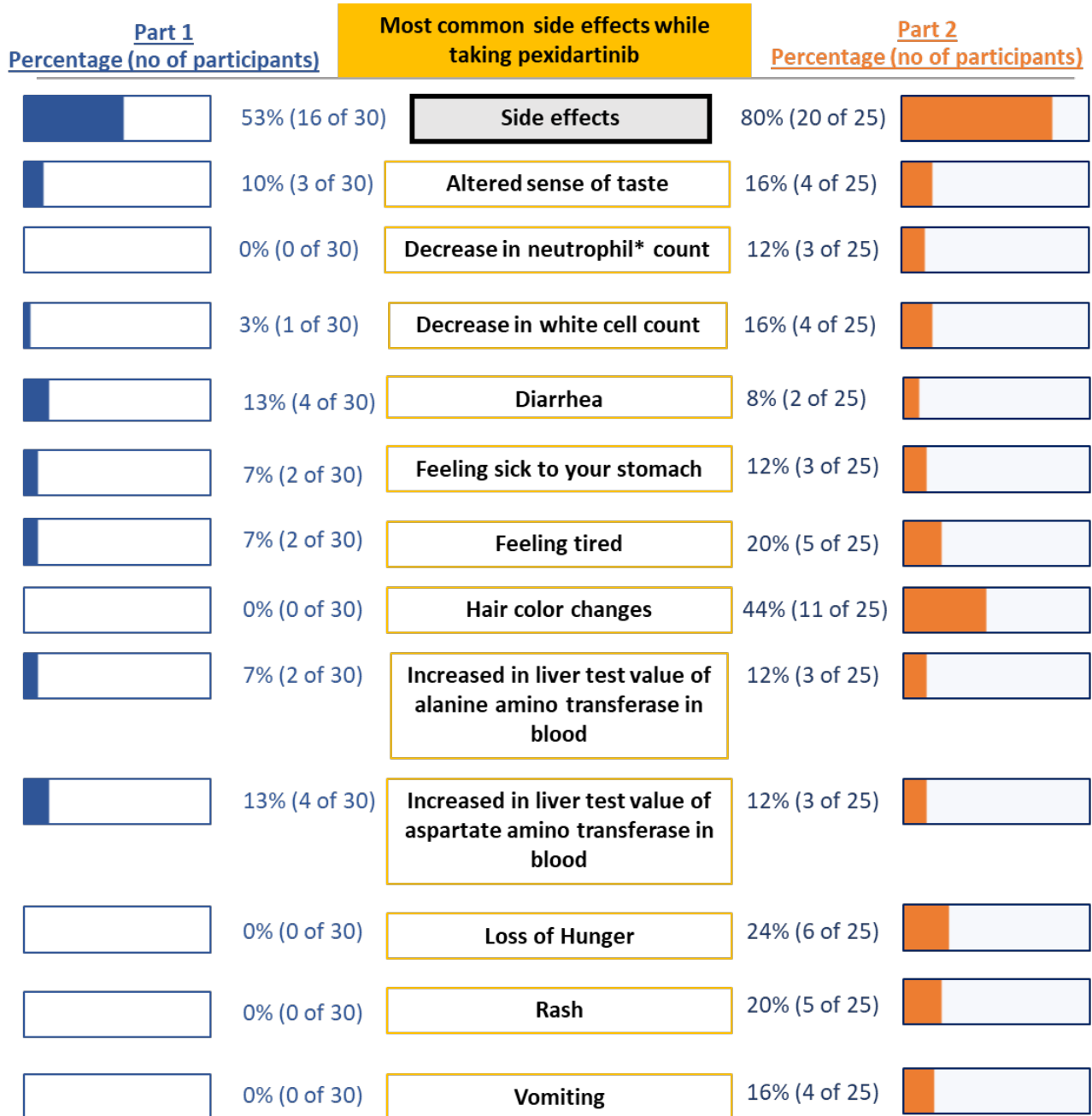
<u>Part 1</u> Percentage (no of participants)	Serious side effects while taking pexidartinib	<u>Part 2</u> Percentage (no of participants)
3% (1 of 30)	Serious side effects	4% (1 of 25)
3% (1 of 30)	Allergic reaction	0% (0 of 30)
0% (0 of 30)	Inflammation of the esophagus*	4% (1 of 25)

Note: * Esophagus is a pipe that takes food from the mouth to stomach

No deaths were reported due to side effects.

How many participants had side effects related to pexidartinib?

The most common side effects, reported by more than 10% of participants in either Part 1 or Part 2 are presented below:



Note: *Neutrophil is a type of white blood cell that fight infections.

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

None of the participants in Part 1 stopped taking pexidartinib due to side effects.

In Part 2, 8% (2 of 25) participants stopped taking pexidartinib because of side effects of increase in liver test value of bilirubin and allergic reaction to the drug.


How was this study useful for patients and researchers?


This study helped researchers learn how pexidartinib affects the blood levels of drugs that are broken down by the liver enzymes CYP3A4 and CYP2C9. Findings from this study may be used in other studies with pexidartinib. Other studies of pexidartinib 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 websites:

 www.clinicaltrials.gov: Use the NCT identifier NCT03291288 in the search field.

 www.clinicaltrialsregister.eu/ctr-search/search: Use the EudraCT identifier 2020-000192-20 in the search field.

Please remember that the results on these websites 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: An Open-Label, Single Sequence, Crossover Drug-Drug Interaction Study Assessing the Effect of Pexidartinib on the Pharmacokinetics of CYP3A4 and CYP2C9 Substrates in Patients

Sponsor: Daiichi Sankyo, Inc.

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