Clinical Study Results

Research Sponsor: AstraZeneca AB

Drug Studied: Adavosertib, also called AZD1775

Study Title: A study to learn if adavosertib affects how other substances get into the blood in participants with advanced solid tumors, and how adavosertib affects the heart

Thank you!

Thank you to the participants who took part in the clinical study for the study drug adavosertib, also called AZD1775.

AstraZeneca AB sponsored this study and thinks it is important to share the results. An independent non-profit organization called CISCRP helped prepare this summary of the study results for you.

If you participated in the study and have questions about the results, please speak with the doctor or staff at your study site.

What is happening with the study now?

The study started in December 2017 and ended in January 2019. The study was stopped early by the study researchers because not enough participants could be included in the study. The sponsor reviewed the data collected when the study ended and created a report of the results. This is a summary of that report.

The study included 33 participants in the United States.

Why was the research needed?

Researchers are looking for a better way to treat patients with advanced solid tumors. Before a drug can be approved for patients to take, researchers do clinical studies to find out how safe it is and how it works.

A solid tumor is a type of cancer that starts in an organ of the body. “Advanced” usually means that the cancer has spread to other parts of the body or has grown beyond the organ where it started. Adavosertib is being developed as a possible treatment for advanced solid tumors.

People with advanced solid tumors often take many different treatments at the same time. In this study, the researchers wanted to learn if taking adavosertib affected the levels of 3 substances in the blood. They also wanted to learn if adavosertib affected the heart.

The 3 substances were caffeine, omeprazole, and midazolam. Caffeine is found in some foods and drinks. Omeprazole is used to treat conditions such as indigestion, heartburn, and acid reflux. Midazolam is used to treat epilepsy and some psychological conditions.

The main questions the researchers wanted to answer in this study were:

- How much caffeine, omeprazole, and midazolam was in the participants’ blood when they were taken with adavosertib?
- Did adavosertib affect the length of time of the participants’ heartbeats?
- What medical problems did the participants have during the study?

The answers to these questions are important to know before other studies can be done that help find out if adavosertib improves the health of people with advanced solid tumors.

The researchers asked for the help of men and women with advanced solid tumors. These participants had tried other treatments, but their tumors were getting worse and there were no other treatments available. The participants were between 41 and 83 years old when they joined the study.

What kind of study was this?

This was an “open-label” study. This means the researchers and the participant knew what the participant was taking.

The doses were measured in milligrams, also known as mg. The doses of each substance and study treatment were:

- 200 mg of caffeine as a tablet
- 20 mg of omeprazole as a tablet
- 2 mg of midazolam as a syrup
- 225 mg of adavosertib as 3 tablets

The study was done in 2 Parts. In **Part A** there were 2 treatment periods. The participants took 2 doses of caffeine, omeprazole, and midazolam and 5 doses of adavosertib.

In **Part B** the participants took 5 doses of adavosertib.

The charts below show the treatments in each part.

Part A

	Treatment Period 1	Treatment Period 2		
Days	**1**	**1**	**2**	**3**
Caffeine, omeprazole, midazolam	✓			✓
Adavosertib in the morning		✓	✓	✓
Adavosertib at night		✓	✓	

Part B

Days	**1**	**2**	**3**	**4**	**5**
Adavosertib in the morning			✓	✓	✓
Adavosertib at night			✓	✓	

What happened during the study?

Before the participants took study treatment, they visited the study site 1 time. This was up to 20 days before they started the study. At this visit, the doctors checked the participants' overall health to make sure that they could join the study. The doctors:

- did a physical exam
- took blood and urine samples
- asked about the participants' medical history, health, and medications

During **Part A** and **Part B**, and after the participants' last study treatment, the doctors also checked the participants' health and took blood and urine samples. They also checked the participants' heart using an electrocardiogram, also called an ECG.

During Part A of the study, the participants visited the study site 2 times. They could choose to stay overnight at each visit. In the first treatment period of **Part A**, the participants took caffeine, omeprazole, and midazolam. Between Treatment Periods 1 and 2, the participants did not take any study treatment for between 7 and 14 days. In the second treatment period, they took caffeine, omeprazole, and midazolam. They also took adavosertib. The participants waited between 7 and 14 days before taking study treatment in **Part B**.

During Part B of the study, the participants visited the study site every day for 5 days. They could choose to stay overnight at each visit. The participants took adavosertib.

After the last study treatment, the participants visited the study site once up to 7 days later. Some of the participants joined another study right away. The participants who did not join the other study visited the study site again up to 30 days later.

What were the results of the study?

This is a summary of the main results from this study overall. The results each participant had might be different and are not in this summary.

Researchers look at the results of many studies to decide which treatments work best and are safest. Other studies may provide new information or different results. Always talk to a doctor before making any treatment change.

The websites listed at the end of this summary may have a full report of the study results.

In **Part A**, 33 participants took the study treatment. In **Part B**, 21 participants took the study treatment.

How much caffeine, omeprazole, and midazolam was in the participants' blood when they were taken with adavosertib?

The researchers wanted to find out if the participants had more caffeine, omeprazole, and midazolam in their blood when they took these with adavosertib.

To answer this question, the researchers measured the amount of caffeine, omeprazole, and midazolam in the participants' blood during **Part A** of the study. They measured:

- the average highest amount of caffeine, omeprazole, and midazolam in the blood. This was measured in nanograms per milliliter, also known as ng/mL.
- the average total amount of caffeine, omeprazole, and midazolam in the blood. This was measured in nanograms per milliliter per hour, also known as ng*h/mL.

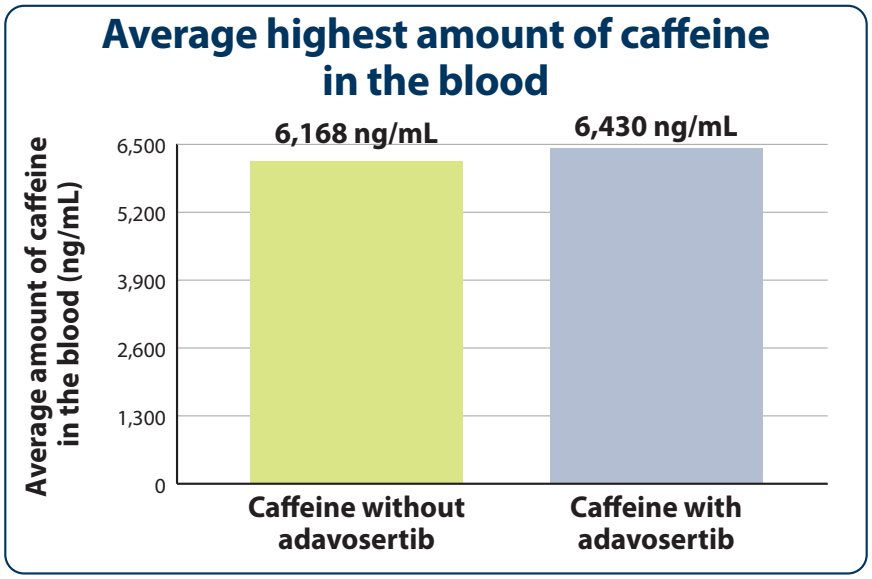
The results of these measurements are shown on the next page.

Caffeine

The researchers found that the average highest amount of caffeine was:

- 6,168 ng/mL when caffeine was taken without adavosertib
- 6,430 ng/mL when caffeine was taken with adavosertib

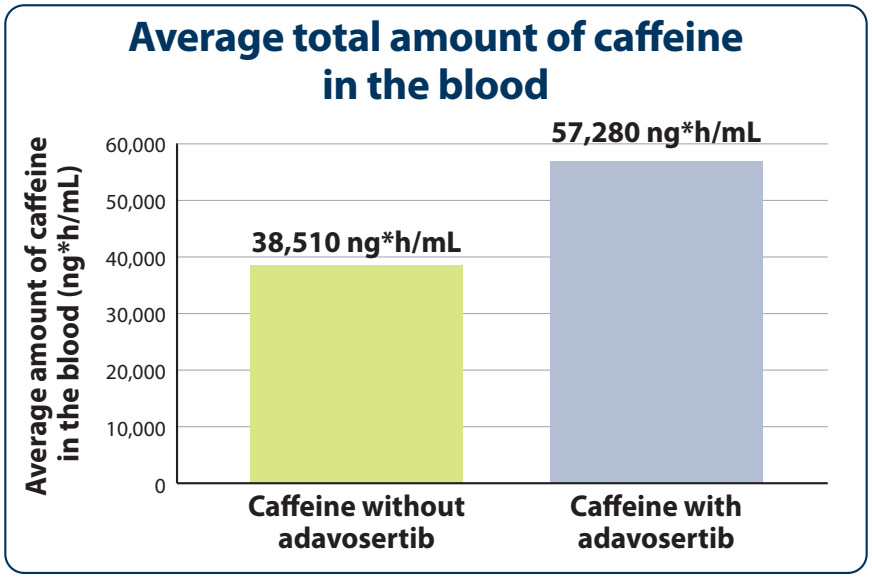
The chart below shows these results.



The average total amount of caffeine was:

- 38,510 ng*h/mL when caffeine was taken without adavosertib
- 57,280 ng*h/mL when caffeine was taken with adavosertib

The chart below shows these results.

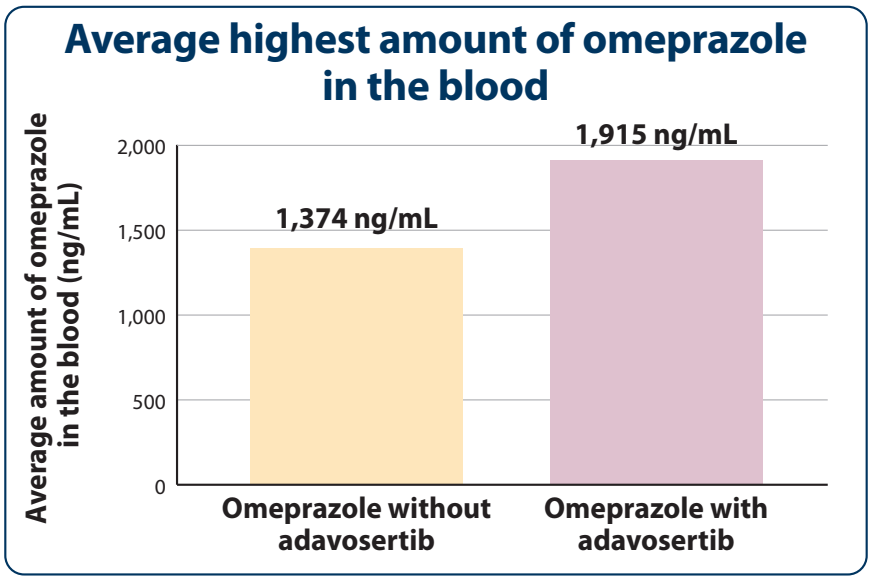


Omeprazole

The researchers found that the average highest amount of omeprazole was:

- 1,374 ng/mL when omeprazole was taken without adavosertib
- 1,915 ng/mL when omeprazole was taken with adavosertib

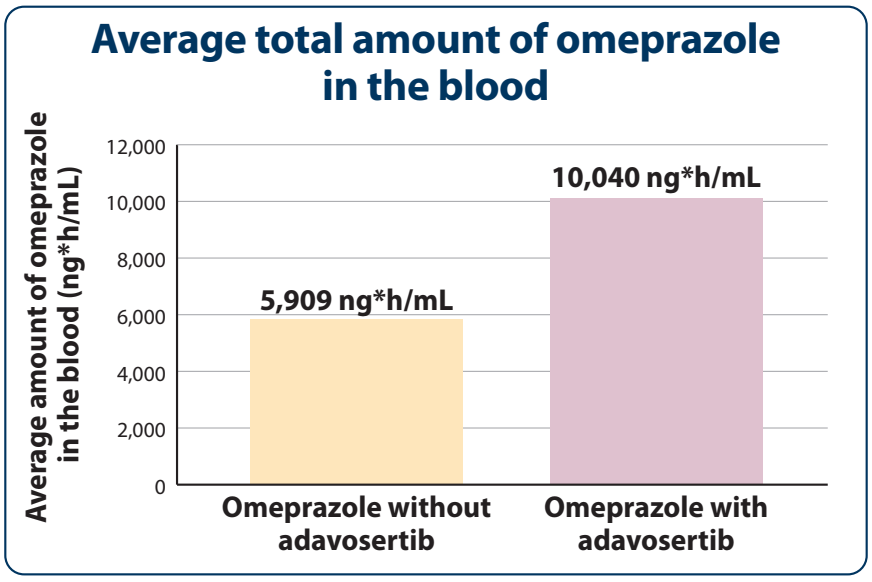
The chart below shows these results.



The average total amount of omeprazole was:

- 5,909 ng*h/mL when omeprazole was taken without adavosertib
- 10,040 ng*h/mL when omeprazole was taken with adavosertib

The chart below shows these results.

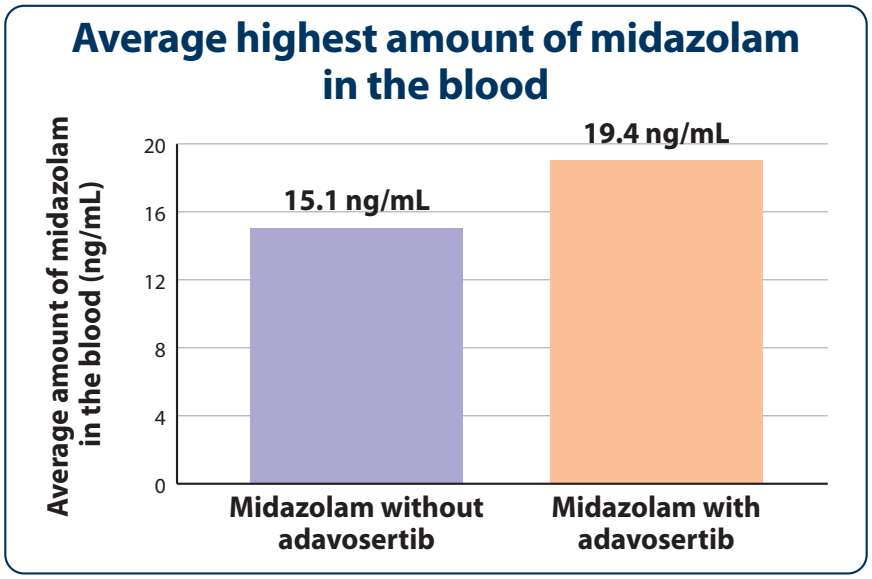


Midazolam

The researchers found that the average highest amount of midazolam was:

- 15.1 ng/mL when midazolam was taken without adavosertib
- 19.4 ng/mL when midazolam was taken with adavosertib

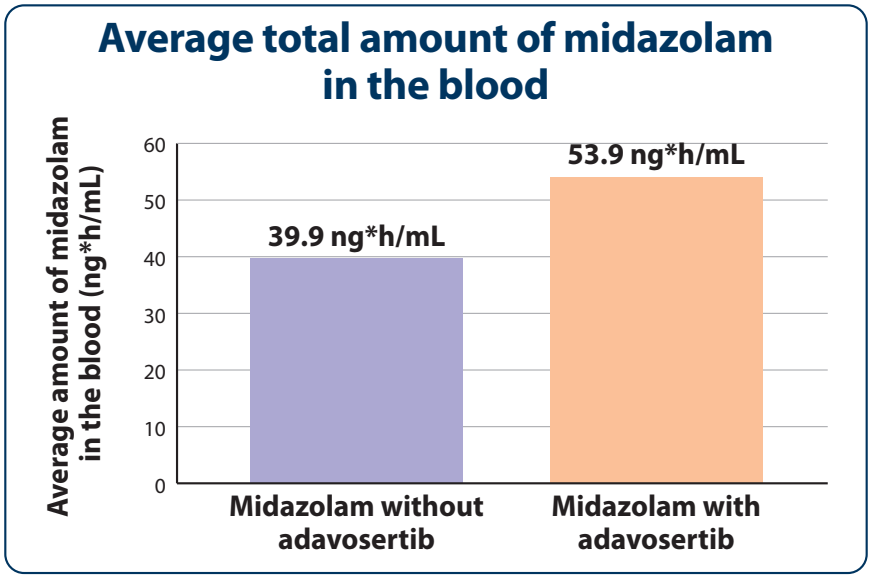
The chart below shows these results.



The average total amount of midazolam was:

- 39.9 ng*h/mL when midazolam was taken without adavosertib
- 53.9 ng*h/mL when midazolam was taken with adavosertib

The chart below shows these results.



Did adavosertib affect the length of time of the participants' heartbeats?

No, adavosertib did not affect the length time of the participants' heartbeats.

To answer this question, the researchers measured the length of time between heartbeats using an ECG during **Part B** of the study. This was done before and after the participants took adavosertib. The difference before and after taking adavosertib was small enough for the researchers to conclude that adavosertib did not affect the length of time of the participants' heartbeats.

What medical problems did participants have during the study?

This section is a summary of the medical problems the participants had during the study that the study doctors thought might be related to the study treatments. These medical problems are called "adverse reactions". An adverse reaction is considered "serious" when it is life-threatening, causes lasting problems, or requires hospital care.

These adverse reactions may or may not be caused by the study treatments. A lot of research is needed to know whether a treatment causes an adverse reaction.

The websites listed at the end of this summary may have other information about adverse reactions or other medical problems that happened during this study.

The results below only include information for the 30 participants who took at least one dose of adavosertib.

How many participants had serious adverse reactions?

There were 3.3% of participants who had serious adverse reactions during the study. This was 1 out of 30 participants.

The serious adverse reactions that happened in this participant during the study were a kidney injury and inflammation of the pancreas.

How many participants had adverse reactions?

Overall, there were 83.3% of participants who had adverse reactions during the study. This was 25 out of 30 participants who took adavosertib.

- There were 63.3% of participants who had adverse reactions in **Part A**. This was 19 out of 30 participants.
- There were 52.4% of participants who had adverse reactions in **Part B**. This was 11 out of 21 participants.

There were 10.0% of participants who stopped taking treatment because of adverse reactions. This was 3 out of 30 participants. This was 1 participant in **Part A**, when they were taking adavosertib with caffeine, omeprazole, and midazolam. This was 2 participants in **Part B**, when they were taking adavosertib.

What adverse reactions did the participants have?

The most common adverse reactions were diarrhea, feeling sick, and vomiting.

The table below shows the most common adverse reactions that happened in more than 2 participants who took adavosertib during the study. There were other adverse reactions, but these happened in fewer participants. The researchers thought that these were related to the study treatment.

Most common adverse reactions in participants who took adavosertib

	Adavosertib (Out of 30 participants)
Diarrhea	60.0% (18)
Nausea	36.7% (11)
Vomiting	30.0% (9)
Weight loss	10.0% (3)
Low numbers of blood cells that fight infection, also called neutrophils	6.7% (2)
Low numbers of blood cells that help clotting, also called platelets	6.7% (2)
Low appetite	6.7% (2)
Dehydration	6.7% (2)
Dizziness	6.7% (2)

How has this study helped patients and researchers?

This study helped researchers learn more about whether adavosertib affects the length of time of heartbeats and the amount of other substances in the blood in participants with advanced solid tumors.

Researchers look at the results of many studies to decide which treatments work best and are safest. This summary shows only the main results from this one study. Other studies may provide new information or different results.

Further clinical studies with adavosertib are planned.

Where can I learn more about this study?

You can find more information about this study on the websites listed below. If a full report of the study results is available, it can also be found here.

- www.clinicaltrials.gov. Once you are on the website, type **"NCT03333824"** into the search box, and click **"Search"**.
- www.AstraZenecaClinicalTrials.com. Once you are on the website, type **"D6014C00006"** into the search box, and click **"Find a Study"**.

Full Trial Title: A Phase I Open-label Study to Evaluate the Effect of Multiple Doses of AZD1775 on the Pharmacokinetics of Substrates CYP3A, CYP2C19, CYP1A2 and to Provide Data on the Effect of AZD1775 on QT Interval in Patients with Advanced Solid Tumours

National Clinical Trials number: NCT03333824

AstraZeneca Protocol Number: D6014C00006

AstraZeneca AB sponsored this study and has its headquarters in Södertälje, Sweden.

The phone number for the AstraZeneca Information Center is +1-877-240-9479.

Thank you!

Clinical study 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 find medical treatments for patients.

CISCRP

The Center for Information & Study on Clinical Research Participation (CISCRP) is a non-profit organization focused on educating and informing the public about clinical research participation. CISCRP is not involved in recruiting participants for clinical studies, nor is it involved in conducting clinical studies.

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