Clinical Study Results

Research Sponsor: AstraZeneca AB

Drug Studied: AZD2014, also called vistusertib

Study Title: A study to learn about the safety of AZD2014 when taken with palbociclib and fulvestrant in participants with breast cancer that has spread

Thank you!

Thank you to the participants who took part in the clinical study for the study drugs AZD2014, also called vistusertib, taken with palbociclib and fulvestrant. Together, they are known as “the study drugs”. All of the participants helped researchers learn more about the study drugs to help people with breast cancer that has spread to other parts of the body.

AstraZeneca AB sponsored this study and thinks it is important to share the results of the study with you and the public. An independent non-profit organization called CISCRP helped prepare this summary of the study results for you. We hope it helps the participants understand and feel proud of their important role in medical research.

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?

Participants were in the study for up to 19 months. The study started in January 2016 and stopped collecting data at the end of March 2018. Some participants have continued receiving treatment within the study.

The sponsor reviewed the data collected when the study stopped collecting results and created a report of the results. This is a summary of that report.

The researchers planned to include up to 259 participants in the study. This study included 54 participants in the United Kingdom and the United States.

Why was the research needed?

Researchers are looking for a better way to treat people with breast cancer that has spread to other parts of the body. 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.

In this study, the researchers wanted to find out if the study drugs AZD2014, palbociclib, and fulvestrant work in participants with a type of tumor called an estrogen receptor positive tumor. If a tumor has an estrogen receptor it means the tumor reacts to hormones found in the body and is expected to grow quicker. They also wanted to find out if the participants had any medical problems during the study.

In people with estrogen receptor positive tumors, a protein called mTOR does not work properly and is too active. This can cause tumor cells to grow out of control. AZD2014 was designed to reduce the activity of mTOR, which would slow the growth of tumor cells.

There are treatments for people with estrogen receptor positive tumors that work in a similar way to AZD2014. But, sometimes when people have received these treatments several times, the treatments stop helping their cancer as much.

In this study, the researchers wanted to learn about the safety of AZD2014 when taken together with palbociclib and fulvestrant. These are existing treatments for estrogen receptor positive tumors that work in a different way than AZD2014. Researchers want to find out if getting these treatments together works to shrink the tumor or slow the growth of the tumor.

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

- Did the study drugs affect the participants' safety results?
- What medical problems did the participants have during the study?

To answer the questions in this study, researchers asked for the help of women with estrogen receptor positive tumors that had spread to other parts of the body. The participants in this study were 36 to 77 years old and had stopped menstruating.

What kind of study was this?

This was a “dose finding” study. This means that the first group of participants started out on a specific dose of study drugs. The doctors carefully looked at the results for these participants. Then, the researchers decided whether to increase or decrease the dose in the next group of participants. Researchers use dose finding studies to learn about the safety of a specific dose before participants are given a different dose.

This was also an “open-label” study. This meant that the participants, the doctors, the study staff, and the researchers knew what doses the participants took. In this study, the participants took AZD2014, palbociclib, and fulvestrant.

Doses were measured in milligrams, also called mg. AZD2014 and palbociclib were tablets that the participants took by mouth. Fulvestrant was given through a needle into the muscle, also called an injection. The participants got their treatment during 28-day time periods called “cycles”.

The researchers planned to have 3 parts to the study, called Part A, Part B, and Part C. But, they decided to change the design during the second part due to a decision by AstraZeneca AB to stop the development of AZD2014. So, only the results from Parts A and B are included in this summary. Each participant was only in Part A or Part B of the study, not both parts.

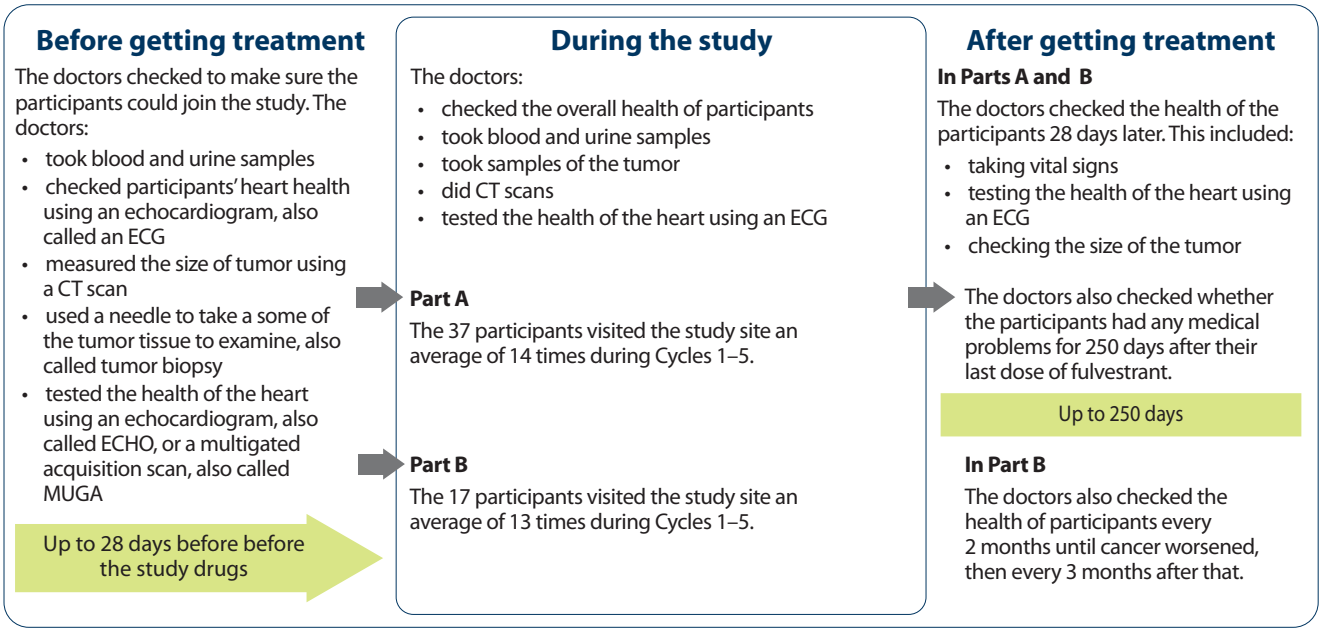
There were 7 treatment groups in total. In Part A, the researchers studied Group 1 through Group 6. In Part B, the researchers studied Group 7. The groups are presented in the order in which they happened during the study.

The table below shows the treatment groups.

Part A	Treatment (28-day cycles)
Group 1 (6 participants)	• Week 1 - 100 mg AZD2014 tablets, twice a day on day 1 and 2 - 100 mg palbociclib tablets once every day for week 1 through week 3 - two 250 mg fulvestrant injections on day 1 • Week 3 (Cycle 1 only): two 250 mg fulvestrant injections on day 1
Group 2 (6 participants)	• Week 1 - 100 mg AZD2014 tablets, twice a day on day 1 and 2 - 75 mg palbociclib tablets once every day for week 1 through week 3 - two 250 mg fulvestrant injections on day 1 • Week 3 (Cycle 1 only): two 250 mg fulvestrant injections on day 1
Group 3 (6 participants)	• Week 1 - 75 mg AZD2014 tablets, twice a day on day 1 and 2 - 75 mg palbociclib tablets once every day for week 1 through week 3 - two 250 mg fulvestrant injections on day 1 • Week 3 (Cycle 1 only): two 250 mg fulvestrant injections on day 1
Group 4 (6 participants)	• Week 1 - 50 mg AZD2014 tablets, twice a day on day 1 and 2 - 75 mg palbociclib tablets once every day for week 1 through week 3 - 250 mg fulvestrant injection on day 1 • Week 3 (Cycle 1 only): two 250 mg fulvestrant injections on day 1
Group 5 (6 participants with low levels of white blood cells called neutrophils)	• Week 1 - 100 mg AZD2014 tablets, twice a day on day 1 and 2 - 100 mg palbociclib tablets once every day - two 250 mg fulvestrant injections on day 1 • Week 3 - 100 mg palbociclib tablets once every day - two 250 mg fulvestrant injections on day 1 (Cycle 1 only)
Group 6 (7 participants with high levels of white blood cells called neutrophils)	• Week 1 - 100 mg AZD2014 tablets, twice a day on day 1 and 2 - 100 mg palbociclib tablets once every day for week 1 through week 3 - two 250 mg fulvestrant injections on day 1 • Week 3 (Cycle 1 only): two 250 mg fulvestrant injections on day 1
Part B	
Group 7 (17 participants)	• Week 1 - 75 mg AZD2014 tablets, twice a day on day 1 and 2 - 75 mg palbociclib tablets once every day for week 1 through week 3 - two 250 mg fulvestrant injections on day 1 • Week 3 (Cycle 1 only): two 250 mg fulvestrant injections on day 1

What happened during the study?

The chart below shows how the study was done.



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. A full list of the questions researchers wanted to answer can be found on the websites listed at the end of this summary. If a full report of the study results is available, it can also be found on these websites.

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 changes.

Did the study drugs affect the participants' safety results?

Yes. Overall, the researchers found that there were some changes in the participants' safety results after they took the study drugs.

To answer this question, the doctors compared the results of the tests and measurements they did before the participants took the study drugs, and throughout the study.

The researchers found that after participants took the study drugs, there were changes in their blood or urine tests that doctors thought were important.

There were changes in the levels of:

- hemoglobin in red blood cells
- overall white blood cell counts
- certain types of white blood cells, called lymphocytes and neutrophils
- platelets, which are needed to help the blood clot
- glucose
- blood clotting proteins
- creatinine
- potassium
- bilirubin
- alanine aminotransferase, a liver enzyme
- aspartate aminotransferase, a liver enzyme

The researchers found that there were no significant changes to the vital signs and ECG tests done throughout the study.

The researchers also collected information about how many "adverse events" the participants had. An adverse event is any medical problem that happens during the study. Adverse events are considered "serious" when they are life-threatening, cause lasting problems, or require hospital care. Adverse events may or may not be caused by the study drugs. This section talks about adverse events that happened during the study. Some of these adverse events are also included in the "What medical problems did participants have during the study?" section.

How many participants had adverse events?

- All of the participants in the study had an adverse event. This was 54 out of 54 participants.
- 18.5% of the participants had at least 1 serious adverse event during the study. This was 10 out of 54 participants.
- 7.4% of the participants stopped taking any study drug because of adverse events. This was 4 out of 54 participants.

What serious adverse events did the participants have?

The table below shows the serious adverse events that the participants had during this study.

Serious adverse events							
	Part A						Part B
Serious adverse events	Group 1 (out of 6 participants)	Group 2 (out of 6 participants)	Group 3 (out of 6 participants)	Group 4 (out of 6 participants)	Group 5 (out of 6 participants)	Group 6 (out of 7 participants)	Group 7 (out of 17 participants)
Sepsis	0.0% (0)	0.0% (0)	16.7% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Urinary tract infection	0.0% (0)	16.7% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Fever and low white blood cell count, neutrophils	16.7% (1)	16.7% (1)	16.7% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Stroke	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	5.9% (1)
Disease of heart valve	0.0% (0)	0.0% (0)	16.7% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Blockage in a blood vessel	0.0% (0)	0.0% (0)	16.7% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Build-up of protein-rich fluid in the abdomen	16.7% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Inflammation of the colon	0.0% (0)	0.0% (0)	16.7% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Difficulty swallowing	16.7% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Rash	0.0% (0)	16.7% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Chest discomfort	0.0% (0)	0.0% (0)	16.7% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Chest pain	0.0% (0)	16.7% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)

11 participants died during the study. All the deaths were due to the worsening of participants' disease. There were no treatment-related deaths during this study.

What were the most common adverse events?

The most common adverse event was low amount of neutrophils, which is a type of white blood cell.

Adverse events that occurred in 15% or more of all the study participants are listed in the table below. Some participants may have had more than 1 adverse event. There were other adverse events, but these happened in fewer participants.

Most common adverse events

	Part A						Part B
Adverse events	**Group 1 (out of 6 participants)**	**Group 2 (out of 6 participants)**	**Group 3 (out of 6 participants)**	**Group 4 (out of 6 participants)**	**Group 5 (out of 6 participants)**	**Group 6 (out of 7 participants)**	**Group 7 (out of 17 participants)**
Low neutrophil white blood cell count	66.7% (4)	50.0% (3)	83.3% (5)	50.0% (3)	83.3% (5)	71.4% (5)	58.8% (10)
Tiredness	83.3% (5)	83.3% (5)	33.3% (2)	16.7% (1)	83.3% (5)	85.7% (6)	52.9% (9)
Nausea	33.3% (2)	66.7% (4)	33.3% (2)	50.0% (3)	66.7% (4)	71.4% (5)	29.4% (5)
Diarrhea	16.7% (1)	66.7% (4)	50.0% (3)	16.7% (1)	50.0% (3)	42.9% (3)	47.1% (8)
Rash	0.0% (0)	66.7% (4)	50.0% (3)	50.0% (3)	33.3% (2)	28.6% (2)	17.6% (3)
Low iron levels in the blood	33.3% (2)	33.3% (2)	16.7% (1)	33.3% (2)	66.7% (4)	14.3% (1)	17.6% (3)
Cough	33.3% (2)	50.0% (3)	50.0% (3)	16.7% (1)	0.0% (0)	28.6% (2)	11.8% (2)
Vomiting	16.7% (1)	16.7% (1)	50.0% (3)	0.0% (0)	16.7% (1)	57.1% (4)	17.6% (3)
Back pain	16.7% (1)	16.7% (1)	16.7% (1)	16.7% (1)	16.7% (1)	14.3% (1)	29.4% (5)
Inflammation of mucus layer in the bowel	33.3% (2)	50.0% (3)	16.7% (1)	16.7% (1)	33.3% (2)	14.3% (1)	5.9% (1)
Urinary tract infection	0.0% (0)	16.7% (1)	33.3% (2)	16.7% (1)	33.3% (2)	42.9% (3)	11.8% (2)
Headache	16.7% (1)	16.7% (1)	33.3% (2)	0.0% (0)	16.7% (1)	42.9% (3)	11.8% (2)
Constipation	16.7% (1)	16.7% (1)	16.7% (1)	16.7% (1)	16.7% (1)	42.9% (3)	5.9% (1)
Blurred vision	16.7% (1)	33.3% (2)	33.3% (2)	16.7% (1)	0.0% (0)	14.3% (1)	11.8% (2)

What medical problems did participants have during the study?

A medical problem that happens during a study is called an “adverse event”. An adverse event that the study doctors think might be related to the study drugs is called an “adverse reaction”. This section is a summary of the adverse reactions that the participants had during the study. 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 drugs. A lot of research is needed to know whether a drug causes an adverse reaction. This section includes the adverse reactions that the doctors thought were related to AZD2014 and to palbociclib, but not to fulvestrant.

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.

How many participants had serious adverse reactions?

- 3.7% of participants had adverse reactions to AZD2014 and palbociclib during the study. This was 2 out of 54 participants. One participant was in Group 2 and one was in Group 3. Both participants had a fever and low neutrophil levels in the blood.
- None of the participants died due to a serious adverse reaction during this study.

How many participants had adverse reactions?

- 94.4% of participants had at least 1 adverse reaction to AZD2014 and palbociclib during the study. This was 51 out of 54 participants.
- 7.4% of participants stopped taking any study drug because of adverse reactions they had during the study. This was 4 out of 54 participants.

What adverse reactions did the participants have?

The most common adverse reaction related to AZD2014 and palbociclib was low neutrophil levels in the blood.

The table below shows the most common adverse reactions related to AZD2014 and palbociclib that happened in more than 15% of participants during the study. There were other adverse reactions, but these happened in fewer participants.

Most common adverse reactions due to AZD2014 and palbociclib during the study

	Part A						Part B
Adverse reaction	**Group 1 (out of 6 participants)**	**Group 2 (out of 6 participants)**	**Group 3 (out of 6 participants)**	**Group 4 (out of 6 participants)**	**Group 5 (out of 6 participants)**	**Group 6 (out of 7 participants)**	**Group 7 (out of 17 participants)**
Low neutrophil white blood cell count	16.7% (1)	50.0% (3)	50.0% (3)	50.0% (3)	83.3% (5)	71.4% (5)	58.8% (10)
Tiredness	66.7% (4)	66.7% (4)	33.3% (2)	0.0% (0)	33.3% (2)	71.4% (5)	41.2% (7)
Nausea	16.7% (1)	50.0% (3)	33.3% (2)	50.0% (3)	66.7% (4)	42.9% (3)	23.5% (4)
Low iron levels in the blood	16.7% (1)	33.3% (2)	0.0% (0)	33.3% (2)	66.7% (4)	14.3% (1)	17.6% (3)
Diarrhea	16.7% (1)	33.3% (2)	33.3% (2)	16.7% (1)	33.3% (2)	28.6% (2)	17.6% (3)
Rash	0.0% (0)	50.0% (3)	50.0% (3)	16.7% (1)	16.7% (1)	0.0% (0)	17.6% (3)

How has this study helped patients and researchers?

This study helped researchers learn more about the safety of AZD2014 when taking with palbociclib and fulvestrant in women with estrogen receptor positive tumors that have spread to other parts of the body.

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 AZD2014 are not currently 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 this website, type **"NCT02599714"** into the search box and click **"Search"**.
- www.clinicaltrialsregister.eu Once you are on the website, click **"Home and Search"**, then type **"2015-003320-30"** in the search box and click **"Search"**.
- www.AstraZenecaClinicalTrials.com. Once you are on the website, type **"D2270C00020"** into the search box and click **"Find a Study"**.

Full Trial Title: A Phase I/II Multicenter Study of the Combination of AZD2014 and Palbociclib on a background of Hormonal Therapy in Patients with Locally Advanced/Metastatic Estrogen Receptor Positive Breast Cancer Comprising a Safety, Pharmacokinetic and Preliminary Efficacy Evaluation followed by a Randomized, Double-Blind, Placebo-controlled, Parallel Group Extension (PASTOR)

National Clinical Trials number: NCT02599714

AstraZeneca Protocol Number: D2270C00020

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 participants.

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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