



CLINICAL STUDY RESULTS

A Study to Learn About the Effect of Strong CYP3A4 Boosters or Blockers on Blood Levels of Tazemetostat (EPZ-6438) in Patients with Advanced Cancer

This study shows that itraconazole increases the levels of tazemetostat while rifampin decreases its levels in the body.

The results shown in this summary are from one clinical study. Other clinical studies may produce different results.

This lay summary has been produced by a company independent of Ipsen. It has been reviewed by employees of Ipsen, and a group of participants or people from a non-scientific background.

What was the study about?

Tazemetostat is a medicine used to treat different cancers like follicular lymphoma (a cancer of the immune system) and epithelioid sarcoma (a cancer of the soft tissues). It works by blocking the action of a protein called EZH2 which is found in the cancer cells.

There are also proteins in the body that help in the breakdown of drugs. Research shows that a protein called Cytochrome P450 3A4 (CYP3A4) plays an important role in breaking down tazemetostat. If CYP3A4 activity is boosted (increased) there is less tazemetostat available in the body and if CYP3A4 activity is blocked (decreased) there is more tazemetostat that is available in the body.

In this study, researchers wanted to see how CYP3A4 affects the levels of tazemetostat in the blood when taken alone, or with drugs that can block or boost CYP3A4 activity. Itraconazole is a drug which blocks or slows down the activity of CYP3A4. Rifampin is a drug which boosts or increases the activity of CYP3A4.

The aim of this study was to learn about the effects of drugs which block or boost CYP3A4 on the levels of tazemetostat in the blood of participants with advanced cancer.

This study took place between April 2020 and April 2023 in the USA and Spain.

This was an “open label” study, which means that both researchers and participants knew what treatment participants were receiving.

Who took part in this study?

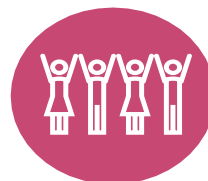
A total of 42 participants were included and treated in the study, with 21 men and 21 women in Part 1 and Part 2.



21
MEN



21
WOMEN



61 YEARS
AVERAGE AGE



To be eligible to take part in the study, participants:

- had to be at least 18 years old
- were expected to live for more than 3 months
- had confirmed advanced malignancies (cancerous tumors) with no standard treatments available
- were up and moving for half of their waking time, and were able to move around and take care of themselves
- were able to swallow
- had completed their prior treatment and surgery before entering the study
- Had normal liver and renal (kidney) function



Participants were not eligible to take part in the study if they:

- had a history of brain or spinal cord cancer, bleeding disorders (difficulty to control bleeding), or were allergic to study drugs
- were already on drugs used in the trial

What treatments were used?

Tazemetostat was given alone, or with either itraconazole or rifampin by mouth with the following dose and timings



PART 1	PART 2
Tazemetostat 400 mg single dose or two times a day and itraconazole 200 mg single dose were given by mouth, either alone or together up until Day 39.	Tazemetostat 800 mg single dose or two times a day and rifampin 600 mg single dose were given by mouth, either alone or together up until Day 26.

Participants had the option to stop treatment at the end of Part 1 or Part 2 or continue treatment with tazemetostat alone. Participants' health was monitored throughout the study up to 30 days after the last dose of tazemetostat.

What was the effect of itraconazole on the levels of tazemetostat in the blood in participants with advanced cancer?

To answer this question, researchers collected blood samples from participants at different timepoints over 3 days to measure the levels of tazemetostat in the body when given with itraconazole.

Researchers determined the maximum levels of tazemetostat in the blood when itraconazole is taken with just one dose of tazemetostat or with two doses of tazemetostat. They also checked how tazemetostat levels change in the blood over time.

Tazemetostat was measured as a maximum level in the blood and as the total amount over a 12-hour period starting from taking the drug to 12 hours later. The maximum levels of tazemetostat in the blood increased by about 2 times when itraconazole was given with tazemetostat single dose or two times a day compared to tazemetostat alone. However, over a 12-hour period, the total levels of tazemetostat increased by about 2 times when itraconazole was given with tazemetostat two times a day, and about 3 times when itraconazole was given with tazemetostat as a single dose.

What was the effect of rifampin on the levels of tazemetostat in the blood in participants with advanced cancer?

To answer this question, researchers collected blood samples from participants at different timepoints over 2 days to measure the level of tazemetostat in the body when given with rifampin.

Researchers determined the maximum level of tazemetostat in the blood when rifampin is taken with just one dose of tazemetostat or with two doses of tazemetostat. They also checked how tazemetostat levels change in the blood over time.

The maximum levels of tazemetostat in the blood decreased by 84% when rifampin was given with tazemetostat 2 times a day compared to tazemetostat alone. Similarly, the total levels of tazemetostat over a 12-hour period also decreased by 84%.

Overall, the study showed that itraconazole increased the levels of tazemetostat in the participant's blood whereas rifampin decreased the levels in the blood.

How did the treatment make participants feel?

During clinical studies, participants are asked to report if they feel unwell, experience any kind of medical event, or notice anything different about their bodies. These are called 'adverse events'. Researchers record *all* adverse events reported by participants, whatever the cause.

If the study doctor thinks an adverse event may be related to the study treatment, it is called a ‘side effect’. A side effect is considered ‘serious’ when it is life-threatening, causes lasting problems, or leads to hospitalization.












- Side effects that are *life-threatening*, that cause lasting problems or require an individual to go to the *hospital*, are considered *serious*.
- One participant experienced 2 serious side effects.
- None of the deaths were related to study treatment.

During the study 28 out of 42 participants (67%) experienced side effects due to tazemetostat, and 8 out of 21 participants (38%) experienced side effects due to itraconazole or rifampin.

- **12 out of 21 participants (57%)** in tazemetostat group and **8 out of 21 participants (38%)** in itraconazole group experienced a side effect in Part 1
- **16 out of 21 participants (76%)** in tazemetostat group and **8 out of 21 participants (38%)** in rifampin group experienced a side effect in Part 2

Tazemetostat was generally well tolerated by participants in both parts. No participant stopped taking part in the study because of a side effect.

The most commonly reported side effects related to tazemetostat that occurred in more than 10% (10 out of 100) of participants are shown in the table below.

Side Effects	Tazemetostat (Part 1) (21 Participants)	Tazemetostat (Part 2) (21 Participants)
Low number of red blood cells	19% (4 out of 21) 	19% (4 out of 21) 
Feeling sick (the desire to vomit)	24% (5 out of 21) 	24% (5 out of 21) 
Diarrhea	5% (1 out of 21) 	14% (3 out of 21) 
Extreme tiredness	14% (3 out of 21) 	33% (7 out of 21) 
Weakness	14% (3 out of 21) 	0% (0 out of 21)
Low number of white blood cells	10% (2 out of 21) 	19% (4 out of 21) 



More information

To learn more about this study, please visit the clinicaltrials.gov website and search for study NCT04537715.

For more information about current treatments available, please speak to your healthcare provider. If you have any questions about this study, please contact the sponsor, Ipsen at:

 clinical.trials@ipson.com

Future research

There is no future research planned on this topic.

Study identification and other information

FULL STUDY TITLE: A Phase I, Open-label, Multi-dose Two-Part Study to Characterize the Effects of a Strong CYP3A4 Inhibitor on the Steady-state Pharmacokinetics of Tazemetostat (EPZ-6438), and the Effects of a Strong CYP3A4 Inducer on the Steady-state Pharmacokinetics of Tazemetostat in Subjects with Advanced Malignancies

STUDY NUMBER: United States: NCT04537715

PROTOCOL: EZH-108

OTHER INFORMATION: Phase I studies can take several months to years to complete and look at the effects and safety of a potential new treatment.

We thank all the volunteers who took part in this study. Without their support, advances in treatments for medical conditions would not be possible.

We would also like to thank the people who took the time to review this document to make it easier for a general audience to read.