Clinical Study Results

This summary reports the results of only one study. Researchers must look at the results of many types of studies to understand if a study medication works, how it works, and if it is safe to prescribe to study participants. The results of this study might be different than the results of other studies that the researchers review.

Sponsor:	Pfizer Inc.
Medicine(s) Studied:	PF-06952229
Protocol Number:	C3881001
Dates of Study:	04 October 2018 to 30 March 2022
Title of this Study:	A Study Looking at the Safety and Levels of PF-06952229 in the Body [A Phase 1 Dose Escalation and Expansion Study Evaluating Safety, Tolerability and Pharmacokinetics of PF-06952229 in Adult Patients With Advanced Solid Tumors]
Date(s) of this Report:	17 March 2023

– Thank You –

If you participated in this study, Pfizer, the Sponsor, would like to thank you for your participation.

This summary will describe the study results. If you have any questions about the study or the results, please contact the doctor or staff at your study site.

Why was this study done?

What is advanced solid tumor cancer?

The study included participants with solid tumor cancers. It had 2 parts: Part 1A and Part 1B.

Solid tumor cancer is a type of cancer that affects parts of the body like the bladder, breast, colorectal area (part of the intestines), head and neck, lung, pancreas, prostate, or ovary.

Participants in this study had solid tumor cancer that was "advanced" or "metastatic". This means that the original cancer has spread from where it originally started and is more difficult to cure.

Part 1A:

Participants in Part 1A had advanced or metastatic solid tumors, that may have high levels of certain biological molecules ("biomarkers"). These biomarkers are called transforming growth factor beta (TGFβ) ("tee-gee-eff beta"). TGFβ activates a chain reaction ("pathway") in the cancer cells that causes the cells to multiply. It can also cause cancer cells to change some of their characteristics. This change is called epithelial-to-mesenchymal transition (or EMT). EMT enables cancer cells to spread from where the tumor started to other parts of the body. It can also stop cancer cells from being recognized by our immune system. The immune system is our body's first defense against disease.

High levels of TGFβ and EMT is a sign that a patient's cancer is becoming metastatic.

Part 1B:

Participants in Part 1B had metastatic castration-resistant prostate cancer (mCRPC). "Castration-resistant" means the cancer no longer responds to treatments that lower hormone called "testosterone". Without testosterone, the prostate cancer cells can't grow, even if they have spread. In participants with mCRPC, the cancer shows signs

of growth even with low levels of testosterone. People with mCRPC need other treatments for their cancer.

What is PF-06952229?

PF-06952229 is a new investigational drug. It is not currently approved for use in the country where the study was held. For this study, that was the United States (US). PF-06952229 is a type of treatment called "TGFβ Receptor I Kinase Inhibitor". The researchers in the study are testing it for the treatment of cancer.

PF-06952229 has a structure which is designed to recognize parts of the TGFβ molecules on the surface of cancer cells. PF-06952229 binds to the TGFβ molecules like a "key and lock" mechanism. PF-06952229 is called "inhibitor" because it stops TGFβ working as usual. This, in turn, stops the cancer cell from changing (see "EMT" explained earlier). Preventing EMT should help to stop/slow the cancer from spreading in the body.

Participants in Part 1A received PF-06952229 alone, and participants in Part 1B received PF-06952229 together with enzalutamide.

Enzalutamide is a type of approved hormone therapy for men with prostate cancer that has spread to other parts of the body. Enzalutamide has been shown to help some men live longer. It can help to treat or delay symptoms, such as pain and bone problems.

What was the purpose of this study?

This study looked at the safety and tolerability of PF-06952229 in participants with advanced solid tumors. "Tolerability" refers to how well participants can tolerate taking the drug.

This was the first time PF-06952229 was given to people. Researchers wanted to find out what the best and safest ("optimal") dose of the drug was. This will help them decide what dose to give to people in future studies.

Researchers did this by giving participants increasing doses of PF-06952229. At each dose level, researchers checked if participants had any dose limiting toxicities (DLTs), before deciding if a higher dose could be given. They also looked at the general safety of different doses.

DLTs are medical problems which usually prevent further increases in the dose of the study medication.

In Part 1A researchers gave increasing doses of PF-06952229 to participants with advanced or metastatic cancers with high levels of TGFβ and/or EMT. This helped them to decide the best dose to give to participants with this type of cancer in future studies. It also helped researchers to decide the best dose(s) of PF-06952229 to give together with enzalutamide in participants with mCRPC, in Part 1B.

Researchers wanted to know:

- **What medical problems did participants have during the study?**
- **What was the optimal dose of PF-06952229 (alone and when given with enzalutamide)?**

What happened during the study?

How was the study done?

The study had 2 parts: Part 1A and Part 1B.

This was an "open-label" study. This means researchers and participants knew what study medication they were receiving.

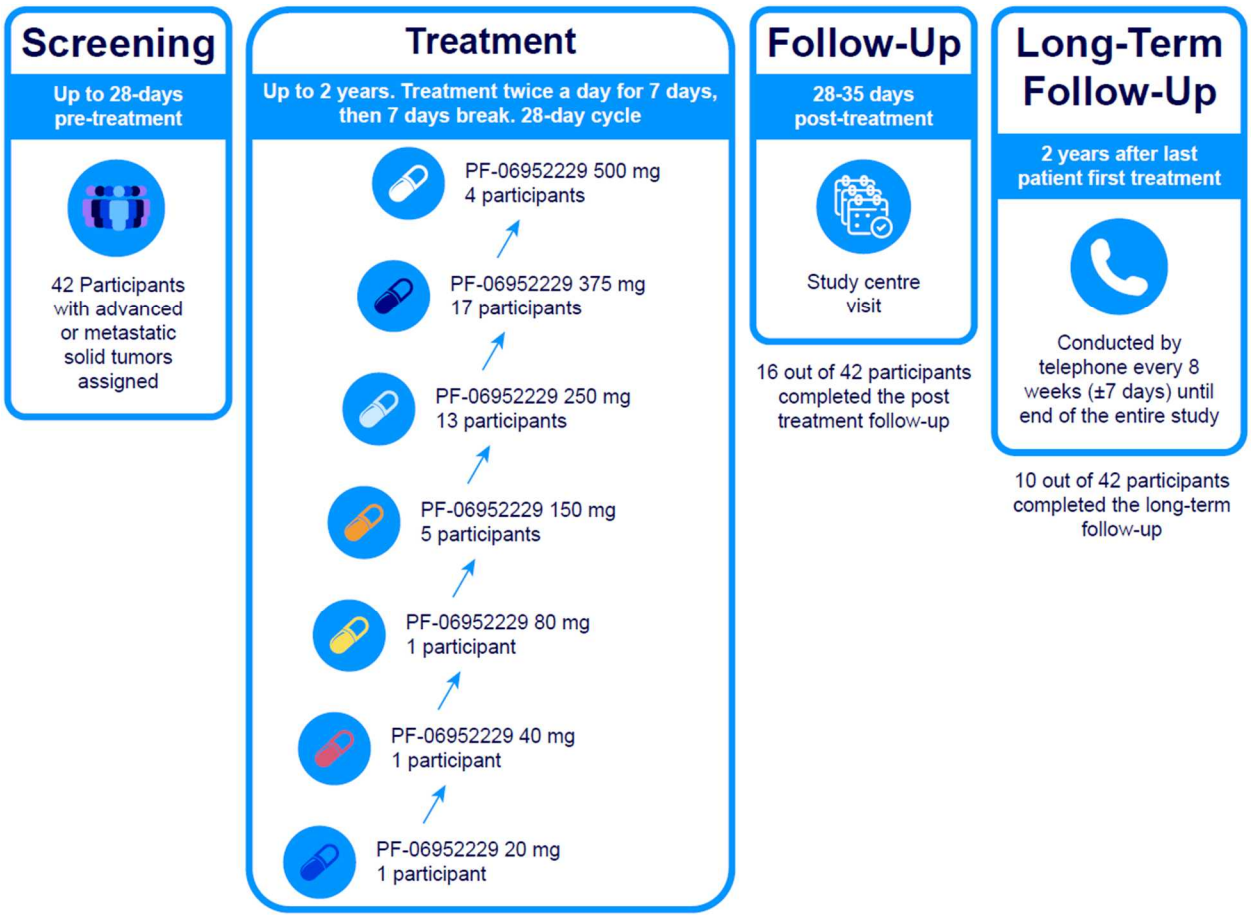
The different visits during Part 1A and Part 1B are shown in Figure 1 and Figure 3, respectively. All participants were "screened" to see if they qualify to be in the study. Participants who qualified for treatment after screening entered the Treatment Phase. They received PF-06952229 in "cycles" as described on the next page (Figure 2) and were monitored continuously. About 28 to 35 days after their last dose, participants had a Follow-up Visit to check their health. Participants also had phone calls about every 8 weeks, for up to 2 years after the last participant who entered the study took their last dose. This was called "Long-term Follow-up".

Part 1A

Participants in Part 1A had advanced or metastatic cancers with high levels of TGFβ and/or EMT. Researchers tested single, increasing doses of PF-06952229 in these participants. The first group of participants were given the lowest dose level; 20 mg of PF-06952229 twice daily.

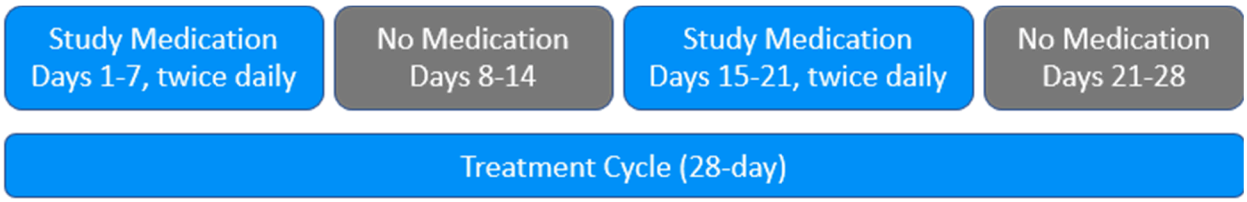
The safety and tolerability of PF-06952229 was assessed and dose was increased for the next group of participants. Each group of participants given a particular dose is called a dosing cohort. This process continued up to the highest dose level tested in Part 1A (500 mg twice daily). A dose was considered safe if there were no DLTs or other medical problems of concern. All doses were taken as tablets by mouth. In total researchers tested 7 different dose levels of PF-06952229 in Part 1A of the study, as shown in Figure 1.

Figure 1. Study Design for Part 1A



At each dose level, participants were treated in 28-day "cycles" as shown in Figure 2. In each cycle, participants took the study medication twice a day; 7 days "on" and 7 days "off" for a total of 28 days. That means that participants took the study medication for 7 days (Days 1 to 7) and then took no study medication for the next 7 days (Days 8 to 14). This was followed again by study medication for 7 days (Days 15 to 21), and then no study medication again for 7 days (Days 22 to 28).

Figure 2. Dosing Cycle of PF-06952229

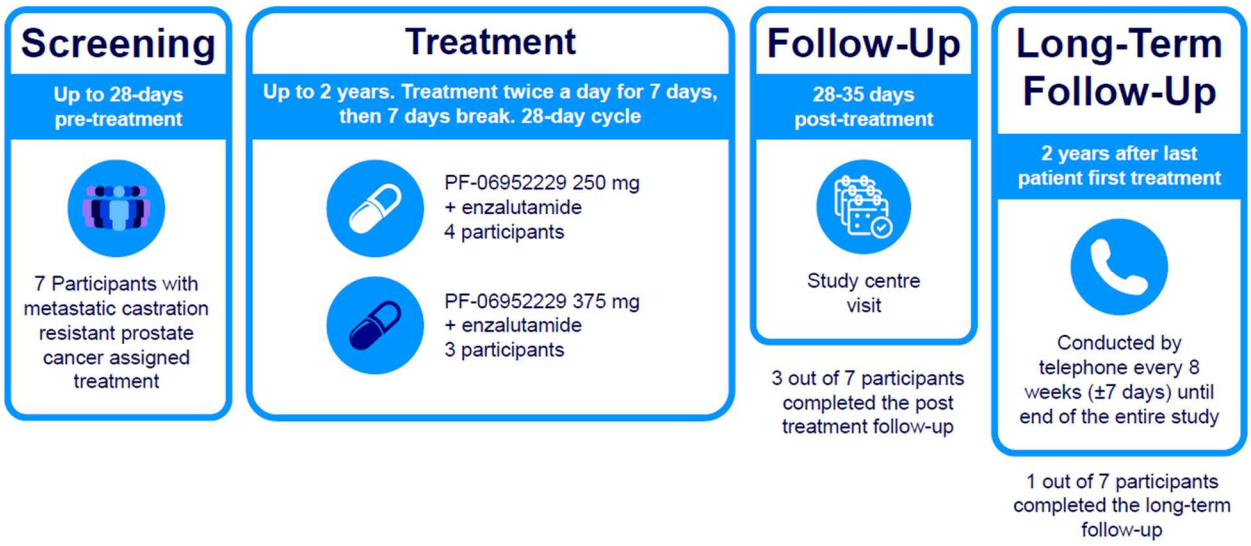


Part 1B

In Part 1B, researchers looked at 2 different doses of PF-06952229, given together enzalutamide in participants with mCRPC.

The starting dose in Part 1B was decided based on results in Part 1A. The first group of participants in Part 1B took PF-06952229 250 mg twice daily. The second group took 375 mg twice daily, as shown in Figure 3.

Figure 3. Study Design for Part 1B



Participants in Part 1B took PF-06952229 28-day cycles as described above for Part 1A and shown in Figure 2. Participants took enzalutamide 160 mg once a day, every day for 28 days in each cycle.

In both Part 1A and Part 1B, participants could continue taking the treatment for more than 1 cycle if the drugs were safely tolerated.

Researchers took samples of blood from participants during the study and measured the amount of PF-06952229 and enzalutamide. Researchers also checked the participants' health during the study.

Researchers then compared the results of participants taking different doses of PF-06952229 alone and PF-06952229 taken together with enzalutamide.

Where did this study take place?

The Sponsor ran this study at 9 locations in the United States.

When did this study take place?

It began on 04 October 2018 and ended on 30 March 2022.

Who participated in this study?

Participants in Part 1A had advanced or metastatic solid tumors with high levels of TGFβ and/or EMT expression.

Participants in Part 1B had mCRPC and were receiving enzalutamide (approved prostate cancer drug).

- There were 42 participants in Part 1A; 37 men and 5 women.
- There were 7 participants in Part 1B, all men.
- All participants across Part 1A and 1B were between the ages of 26 and 88 years.

Part 1A:

The 42 participants who started Part 1A of the study stopped treatment due to the following reasons:

- Participants' cancer got worse: (40%, 17 out of 42 participants)
- Overall health deteriorated or got worse (19%, 8 out of 42 participants)
- A medical problem meant that the participant or their doctor thought it was best for the participant to stop treatment (14%, 6 out of 42 participants)
- Other reasons (14%, 6 out of 42 participants)
- Participant wanted to stop treatment (12%, 5 out of 42 participants)

Part 1B:

Of the 7 participants who started Part 1B of the study, no participants finished the Treatment Phase. Reasons why participants did not complete the Treatment Phase were:

- Participants' cancer got worse: (43%, 3 out of 7 participants)
- A medical problem meant that the participant or their doctor thought it was best for the participant to stop treatment: (29%, 2 out of 7 participants)
- Overall health deteriorated or got worse (14%, 1 out of 7 participants)
- Participant wanted to stop treatment (14%, 1 out of 7 participants)

How long did the study last?

The time participants were in the study, depended on their number of treatment cycles and follow-up time. The researchers planned to monitor the health of participants for up to 2 years from the time that the last participant who entered the study received their first treatment.

The entire study took about 3 years and 6 months to complete.

When the study ended in March 2022, the Sponsor created a report of the results. This is a summary of that report.

What were the results of the study?

How safe and well tolerated was PF 06952229 (alone or together with enzalutamide)?

Researchers looked at the medical problems that participants had in the 28 days after their first dose of PF-06952229 (Cycle 1) to see if there were DLTs. Researchers also looked at results of laboratory tests to see if there were any abnormal results of

concern. This helped researchers decide if each dose was safe and well tolerated, and if it was safe to give the next group of participants a higher dose of the drug.

Medical problems throughout the whole of the study are discussed in full in the next section of this document.

Did participants who took PF-06952229 (alone or together with enzalutamide) have dose-limiting toxicities (DLTs)?

- In Part 1A of this study, 3 out of the 35 participants (9%) who were assessed for DLTs, experienced medical problems that were considered to be DLTs. All 3 participants were in the 375 mg cohort, and experienced medical problems that were rated as Grade 3, which means that study doctors considered the events to be severe or medically significant.
  - One participant experienced Grade 3 anemia (low red blood cell count) (Study Day 28 to 41). The study treatment was interrupted for this participant.
  - One participant experienced a Grade 3 bleeding brain tumor (Study Day 7 to 19), and their participation in the study was stopped.
  - One participant experienced Grade 3 anemia and Grade 3 low blood pressure, (both Study Day 21 to 25), and their participation in the study was stopped.
- No participants in Part 1B who received PF-06952229 250 mg or 375 mg twice daily together with enzalutamide, experienced any DLTs during Cycle 1 of treatment.

Did participants who took PF-06952229 (alone or together with enzalutamide) experience any medically important medical problems?

Tumor bleeding events:

- In Part 1A of the study, 2 participants had medical problems of bleeds in their tumors, as follows:
  - One participant in the 250 mg cohort had a medical problem of a bleed in their liver.
  - One participant in the 375 mg cohort had a medical problem of a bleed in their brain tumor.
- Researchers considered both medical problems to be serious and possibly related to taking PF-06952229.

Other bleeding events:

Part 1A:

In Part 1A, bleeding events shown below were reported. Most events were reported in the 375 mg and 500 mg cohorts.

3 participants	2 participants each	1 participant each
• Nosebleed	• Bleeding in mouth • Blood in urine	• Bleeding in gums • Bleeding in hemorrhoids • Bleeding in voice box • Vomiting blood

Part 1B:

In Part 1B, 3 bleeding events were reported: blood in urine (1 participant each in the PF-06952229 250 mg + enzalutamide cohort and PF-06952229 375 mg + enzalutamide cohort), and rectal bleeding (1 participant in the PF-06952229 375 mg + enzalutamide cohort), as shown below:

2 participants	1 participant
• Blood in urine	• Rectal bleeding

Anemia (low red blood cell count):

Anemia was one of the medical problems that was reported most often after taking PF-06952229. Researchers considered it to be a potential risk for people taking the drug.

Part 1A:

Figure 4 shows the number of participants with anemia in Part 1A, as follows:

1. Eleven (11) out of 42 participants (26%) overall had anemia after taking PF-06952229.
2. Eight (8) out of 42 participants (19%) had anemia that researchers might be related to taking PF-06952229.
3. Two (2) out of 42 participants (5%) had anemia that researchers thought was serious.

Figure 4. Number of Participants with Anemia (Part 1A)

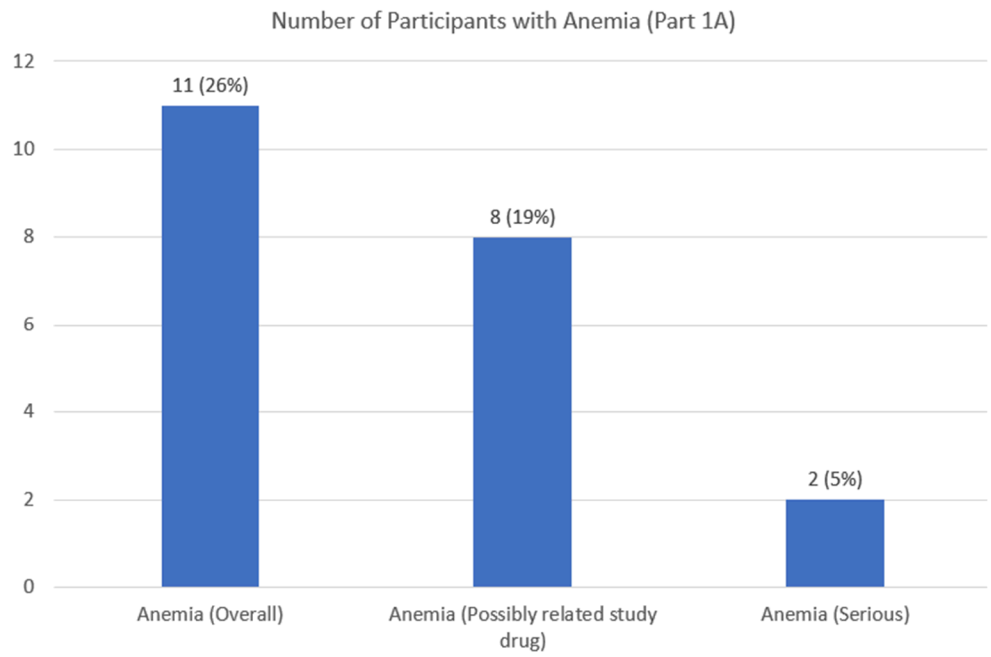
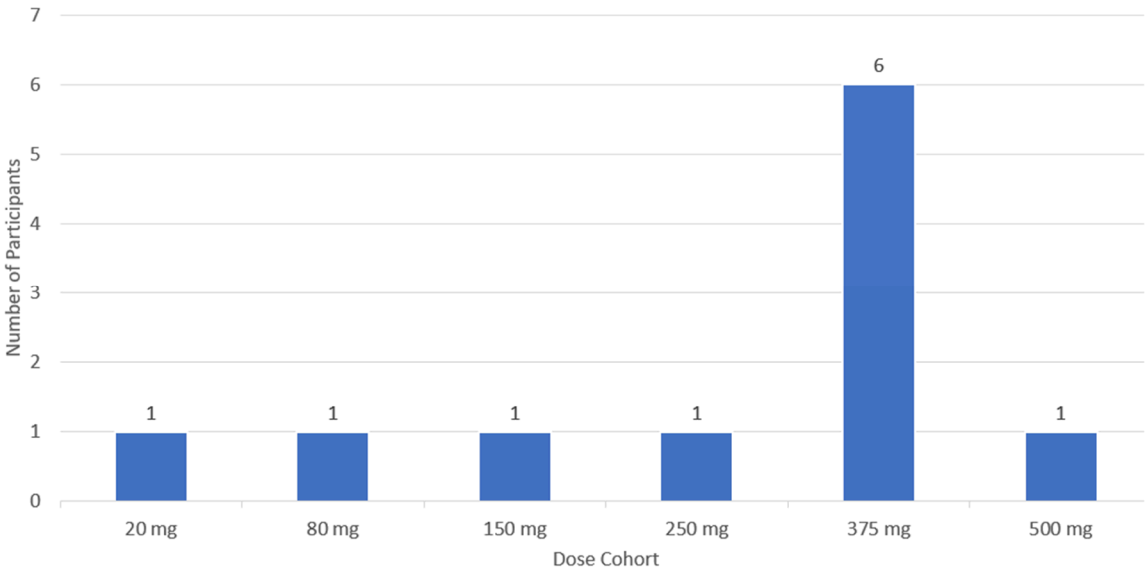


Figure 5 shows the number of participants with anemia by dose group.

Figure 5. Number of Participants with Anemia (Part 1A) by Dose Cohort



Six (6) out of 42 participants (14%) had Grade 3 anemia; 3 participants in the 375 mg cohort and 1 participant each in the 20 mg, 150 mg, and 250 mg cohorts.

Serious anemia was reported for 1 participant each in the 150 mg cohort and 1 in the 375 mg cohort.

Two out of 42 participants (5%) stopped taking PF-06952229 due to medical problems of anemia that were considered to be possibly related to taking the study medication. Both were in the 375 mg cohort.

In summary, most of the medical problems of anemia in Part 1A, including those that were Grade 3 or "severe" and those that were thought to be serious, were seen in the 375 mg cohort.

Part 1B:

Medical problems of anemia events were reported in 2 out of 7 participants (29%): 1 each in the PF-06952229 250 mg + enzalutamide cohort and PF-06952229 375 mg + enzalutamide cohort. No medical problems of anemia in Part 1B were considered serious, or possibly related to taking PF-06952229. None of the events of anemia caused participants to permanently stop taking PF-06952229.

Did participants given PF-06952229 (alone or together with enzalutamide) experience any medically important abnormal laboratory results?

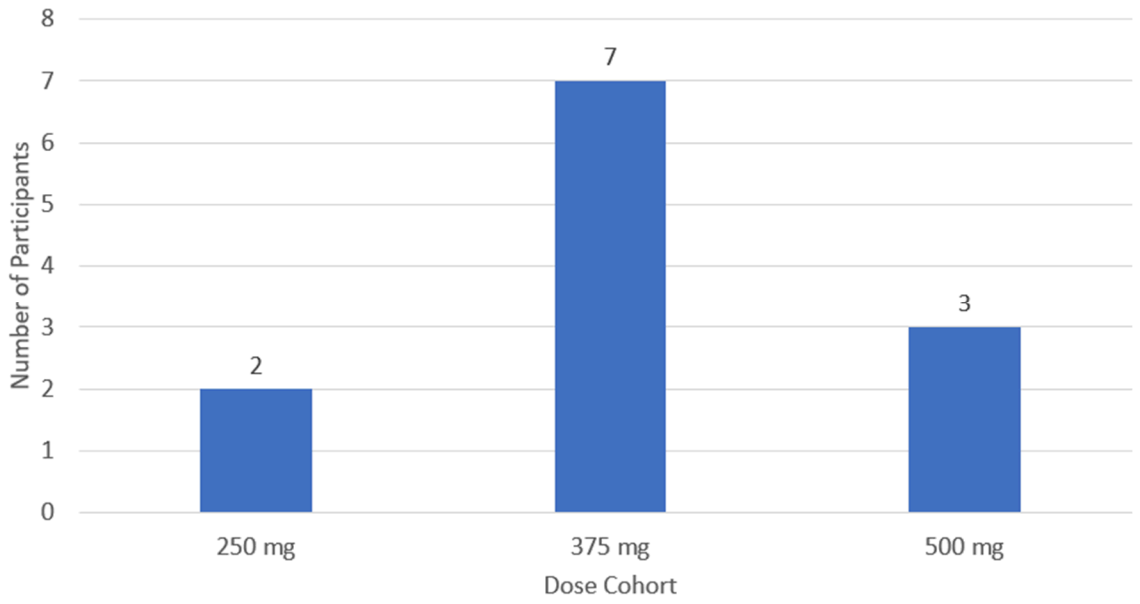
Increases in some liver enzymes (called alanine amino transferase or "ALT" and aspartate aminotransferase or "AST") were commonly observed during the study.

Part 1A:

In Part 1A, 12 out of 42 participants (29%) experienced medical problems of ALT and AST increased. Figure 6 shows the number of participants with ALT and AST increased by dose cohort. The highest number of participants was seen in the

375 mg cohort. Six of the 12 participants had Grade 3 ALT increased and 2 participants had Grade 3 AST increased.

Figure 6. Number of Participants with ALT or AST Increased by Dose Cohort (Part 1A)



Overall, 10 out of 42 participants (24%) had medical problems of ALT and AST increased were considered possibly related to taking PF-06952229. Four of the 10 participants had events that were judged to be Grade 3 or "severe".

No serious medical problems of ALT or AST increased were reported and no participants stopped taking PF-06952229 due to increased ALT or AST in Part 1A.

Part 1B:

In Part 1B, no serious medical problems of ALT increased, or AST increased were reported. One participant (14%) (in the PF-06952229 250 mg + enzalutamide cohort) had a medical problem of ALT increased (Grade 3) and AST increased

(Grade 2, which means it was of "moderate" severity) and was permanently discontinued from the study.

What was the maximum tolerated dose and recommend dose of PF-06952229?

The researchers were not able to answer this question in the current study.

This does not mean that everyone in this study had these results. This is a summary of just some of the main results of this study. Other studies may have different results.

What medical problems did participants have during the study?

The researchers recorded any medical problems the participants had during the study. Participants could have had medical problems for reasons not related to the study (for example, caused by an underlying disease or by chance). Or, medical problems could also have been caused by a study treatment or by another medicine the participant was taking. Sometimes the cause of a medical problem is unknown. By comparing medical problems across many treatment groups in many studies, doctors try to understand what effects a study medication might have on a participant.

All 42 (100%) participants in Part 1A and all 7 (100%) participants in Part 1B of this study had at least 1 medical problem. A total of 6 participants in Part 1A and 2 participants in Part 1B left the Treatment Phase of the study because of medical problems. The most common medical problems – those reported by more than 10% of participants in Part 1A and more than 1 participant in Part 1B – are described below.

Below are instructions on how to read Table 1 and Table 2.

Instructions for Understanding Table 1.

- The **1st** column of Table 1 lists medical problems that were commonly reported during Part 1A of the study. All medical problems reported by more than 10% of participants are listed.
- The **2nd** column tells how many of the 42 participants in Part 1A taking the study medication reported each medical problem. Next to this number is the percentage of the 42 participants in Part 1A taking the study medication who reported the medical problem.
- Using these instructions, you can see that 16 out of the 42 participants in Part 1A taking the study medication reported nausea.

Instructions for Understanding Table 2.

- The **1st** column of Table 2 lists medical problems that were commonly reported during Part 1B of the study. All medical problems reported by more than 1 participants are listed.
- The **2nd** column tells how many of the 7 participants in Part 1B taking the study medication reported each medical problem. Next to this number is the percentage of the 7 participants in Part 1B taking the study medication who reported the medical problem.
- Using these instructions, you can see that 2 out of the 7 participants in Part 1B taking the study medication reported anemia (low red blood cell count), joint pain, back pain, constipation, blood in urine, headache and low phosphate level in blood.

Table 1. Commonly reported medical problems reported for more than 10% of study participant in Part 1A	
Medical Problem	**PF 06952229 (42 Participants)**
Nausea	16 out of 42 participants (38%)
Headache	13 out of 42 participants (31%)
Increased liver enzyme (ALT) in blood	12 out of 42 participants (29%)
Increased liver enzyme (AST) in blood	12 out of 42 participants (29%)
Anemia (low red blood cell count)	11 out of 42 participants (26%)
Vomiting	10 out of 42 participants (24%)
Tiredness	9 out of 42 participants (21%)
Constipation	6 out of 42 participants (14%)
Cough	6 out of 42 participants (14%)
Decreased appetite	6 out of 42 participants (14%)
Dehydration	6 out of 42 participants (14%)

Table 1. Commonly reported medical problems reported for more than 10% of study participant in Part 1A	
Medical Problem	PF 06952229 (42 Participants)
Joint pain	5 out of 42 participants (12%)
Diarrhea (loose stools)	5 out of 42 participants (12%)
Difficulty breathing	5 out of 42 participants (12%)
Low phosphate level in blood	5 out of 42 participants (12%)
Stuffy nose	5 out of 42 participants (12%)

Table 2. Commonly reported medical problems reported for more than 1 study participant in Part 1B	
Medical Problem	PF 06952229+Enzalutamide (7 Participants)
Anemia (low red blood cell count)	2 out of 7 participants (29%)
Joint pain	2 out of 7 participants (29%)
Back pain	2 out of 7 participants (29%)

Table 2. Commonly reported medical problems reported for more than 1 study participant in Part 1B	
Medical Problem	**PF 06952229+Enzalutamide (7 Participants)**
Constipation	2 out of 7 participants (29%)
Blood in urine	2 out of 7 participants (29%)
Headache	2 out of 7 participants (29%)
Low phosphate level in blood	2 out of 7 participants (29%)

Did study participants have any serious medical problems?

A medical problem is considered "serious" when it is life-threatening, needs hospital care, or causes lasting problems.

Part 1A:

Eleven (11) participants in Part 1A (26%, or 11 out of 42 participants) had serious medical problems after being treated with PF-06952229. Most serious medical problems were only reported in 1 participant each. Also, most were not considered related to treatment with PF-06952229.

These events included:

- Stomach pain and anemia (low red blood cell count) (both 2 participants [5%] each),
- Lung failure, joint pain, back pain, constipation, dehydration, disease progression (cancer getting worse), fracture, vomiting blood, bleeding in liver, low blood sodium, low blood pressure, bleeding in brain tumor, bleeding in voice box, bleeding in mouth, pain, pneumonia, fever, and sepsis (blood stream infection) (all 1 participant [2%] each).

Researchers thought 6 of the serious medical problems might be related to taking PF-06952229.

These events were serious medical problems of:

- Anemia (low red blood cell count) in 1 participant in the 150 mg cohort.
- Bleed in liver in 1 participant in the 250 mg cohort.
- Anemia (low red blood cell count), fever and low blood pressure in 1 participant in the 375 mg cohort.

- Bleeding brain tumor in 1 participant in the 375 mg cohort.

One participant in the 150 mg cohort in Part 1A died 16 days after last dose of study medication, due their cancer getting worse.

Part 1B:

No participants in Part 1B had any serious medical problems.

Where can I learn more about this study?

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

For more details on your study protocol, please visit:

The full scientific report of this study is available online at:

www.clinicaltrials.gov — Use the study identifier **NCT03685591**

www.pfizer.com/research/research_clinical_trials/trial_results — Use the protocol number C3881001

Please remember that researchers look at the results of many studies to find out which medicines can work and are safe for patients.

Again, if you participated in this study,
thank you for volunteering.
We do research to try to find the
best ways to help patients, and you helped
us to do that!