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 patients. 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-07258669

Protocol Number: C4541003

Dates of Study: 08 November 2021 to 27 July 2023

Title of this Study: A Study of PF-07258669 In Healthy Adult Participants

[A Phase 1, Randomized, Double-Blind, Sponsor-Open, Placebo-Controlled Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacokinetic Interaction With Midazolam of Multiple Ascending Oral Doses of PF-07258669 in Healthy Non-Japanese and Japanese Adult Participants]

Date of this Report: 15 September 2024

– 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 geriatric anorexia?

Geriatric anorexia refers to the reduced desire to eat food and decreased food intake in the elderly. Geriatric anorexia can lead to lack of nutrients in the body, reduced muscle size, weakness, and increased risk of death.

Melanocortin-4 receptor (or "MC4R") is a protein in the brain that is important for controlling the desire to eat. Researchers think that too much activity of MC4R in the brain may contribute to geriatric anorexia.

What is PF-07258669?

PF-07258669 is being developed to help treat geriatric anorexia. At the time of this study, it was not approved to treat any diseases or health conditions. It is provided as a tablet and is taken by mouth.

PF-07258669 works by blocking the activity of MC4R in the brain. Researchers think this may increase the desire to eat food and increase food intake. This could help improve the symptoms of geriatric anorexia.

What was the purpose of this study?

This study had 2 parts: Part A and Part B. Both parts enrolled healthy adults.

The main purpose of Part A of the study was to learn more about the safety and tolerability (how someone feels while taking the medicine) of PF-07258669 when given at multiple, increasing doses.

The main purpose of Part B of the study was to learn how PF-07258669 affected midazolam levels in the body when they were taken together. This will help researchers determine if PF-07258669 changes the levels of medicines that are removed from the body in ways similar to midazolam.

Researchers think that this may be helpful information if PF-07258669 is tested in future studies.

Researchers wanted to know:

- **How did participants feel and what medical problems did they have after taking PF-07258669?**
- **How does PF-07258669 affect midazolam levels in the body?**

What happened during the study?

How was the study done?

First, study doctors checked if potential participants met the requirements to be in the study. Participants who met the requirements to be in the study joined either Part A or Part B of the study.

Part A of the Study

Researchers gave increasing doses of PF-07258669 to participants to learn how safe and tolerable it was. Researchers also assigned participants to eat 1 of 3 pre-specified diets during the study because they wanted to study PF-07258669 when given with diets that differed in terms of the number of calories and the amount of fat and carbohydrates.

Researchers tested 7 different doses (or "dose levels") of PF-07258669: 2 mg, 3 mg, 6 mg, 20 mg, 60 mg, 125 mg, and 180 mg. Each dose was given 3 times a day (every 8 hours) by mouth for a total of 14 days, except for Day 14, in which participants were only given 1 dose in the morning. They tested each dose level one at a time and did not start giving the next dose level to the next group of participants until the previous dose level

was complete. Figure 1 below shows the order that dose levels were given.

Participants were then randomly assigned to receive either PF-07258669 or placebo. A placebo does not have any medicine in it, but it looks just like the study medicine. This was done to help researchers try to understand if medical problems that the participants had during the study could be related to the study medication or related to something else.

Each participant received only 1 dose level of PF-07258669 or placebo treatment during Part A of the study.

The diets and dose levels are described below:

<u>High carbohydrate-high calorie diet:</u>

- Participants in this group ate a diet that was about 30% fat, 15% protein, and 55% carbohydrates. There was no limit for the calories they could eat per day.
- Participants were randomly assigned to receive one of the following treatments:
    - Placebo (6 participants)
    - 3 mg PF-07258669 (8 participants)
    - 2 mg PF-07258669 (8 participants)
    - 6 mg PF-07258669 (7 participants)

<u>Standard diet:</u>

- Participants in this group ate a diet that was less than 3200 calories per day. Their diets were about 30% fat, 15% protein, and 55% carbohydrates.

- Participants were randomly assigned to receive one of the following treatments:
    - Placebo (10 participants)
    - 6 mg PF-07258669 (8 participants)
    - 20 mg PF-07258669 (8 participants)
    - 60 mg PF-07258669 (8 participants)
    - 125 mg PF-07258669 (8 participants)
    - 180 mg PF-07258669 (8 participants)
- 6 Japanese participants who joined the study ate this diet and were assigned to receive either:
    - Placebo (1 participant)
    - 180 mg PF-07258669 (5 participants)

<u>High fat-high calorie diet:</u>

- Participants in this group ate a diet that was less than 4500 calories per day. Their diets were about 55% fat, 15% protein, and 30% carbohydrates.
- Participants were randomly assigned to receive either:
    - Placebo (12 participants)
    - 180 mg PF-07258669 (12 participants)

In Part A of the study, the participants and researchers at the study site did not know who took different doses of PF-07258669 and who took placebo. This is known as a “double-blind” study.

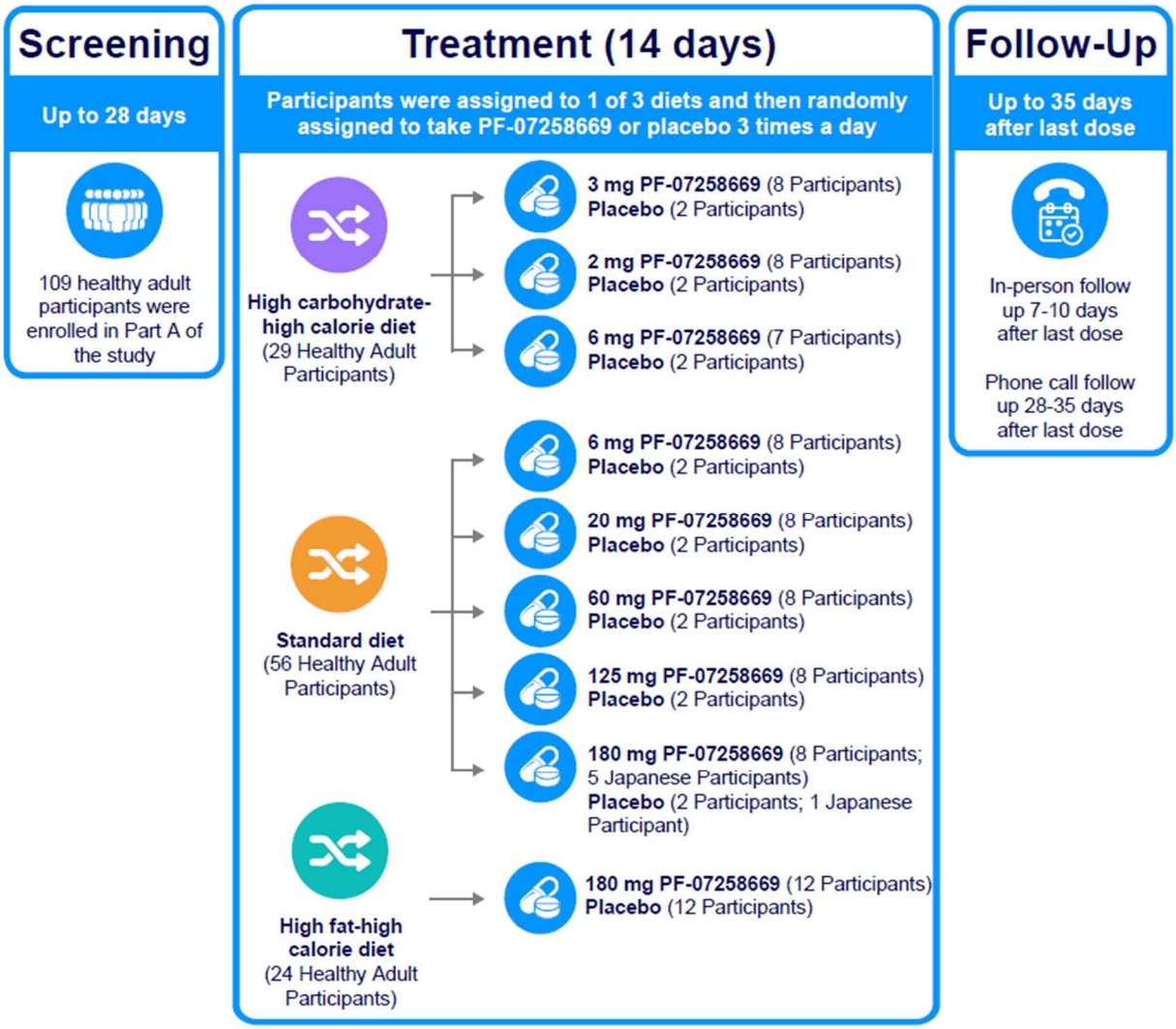
During the study, researchers checked the participants' health, asked them how they were feeling, and asked if they had any medical problems.

Participants returned to the study site for a follow-up visit 7-10 days after the last dose of the treatment period. Study site staff also called participants 28-35 days after the last dose of the treatment. These visits were done to check the health of participants.

Researchers then compared the safety and tolerability results of participants taking different doses of the study medication to the results of participants taking a placebo.

The design of Part A of the study is shown in Figure 1 below.

Figure 1. Study Design of Part A



*Note that 1 dose level was tested at a time and generally the testing was increased from lower to higher doses. Each dose level did not start until the previous dose level testing was complete.

Part B of the Study

In Part B of the study, researchers tested how taking PF-07258669 and midazolam together affected midazolam levels in the body of healthy adults.

Part B of the study had 2 periods: Period 1 (3 days long) and Period 2 (11 days long). Participants participated in both periods. During these periods, participants ate the standard diet described above in Part A.

Period 1:

- During this period, participants took a single 1 mg dose of midazolam (as a liquid taken by mouth) on Day 1.
- Researchers took samples of blood from participants during Period 1 and measured the amount of midazolam.

Period 2:

- During this period, participants took 180 mg PF-07258669 three times a day (every 8 hours) for 10 days. On Day 2 and Day 10 of Period 2, participants took a single 1 mg dose of midazolam with the morning dose of PF-07258669.
- Researchers took samples of blood from participants during Period 2 and measured the amount of midazolam.

During both periods, researchers also checked the participants' health during the study and asked them how they were feeling.

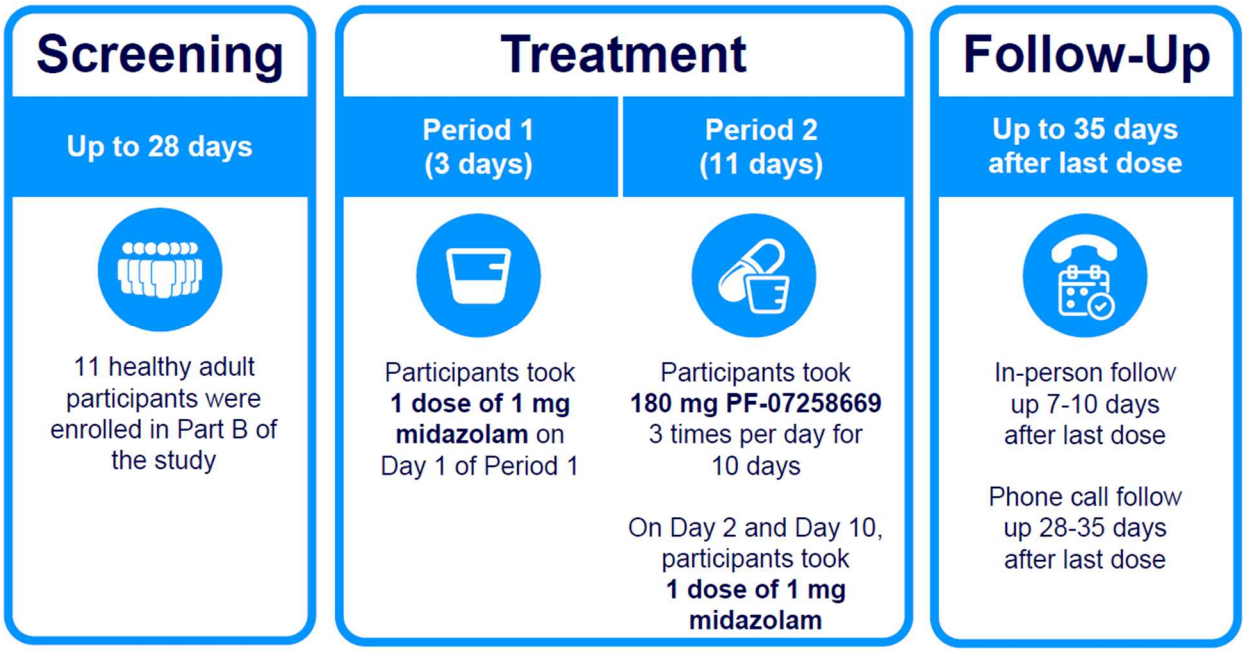
Participants returned to the study site for a follow-up visit 7-10 days after the last dose of Period 2. Study site staff also called participants 28-35 days after the last dose of Period 2. These visits were done to check the health of participants.

Researchers then compared the results of taking the midazolam alone to the results of taking midazolam and PF-07258669 together.

In Part B of the study, the participants and researchers knew that the participants were taking midazolam and PF-07258669. This is known as an “open-label” study.

The design of Part B of the study is shown in Figure 2 below.

Figure 2. Study Design of Part B



*Note that all 11 participants in Part B participated in both Period 1 and Period 2 of the treatment period.

Where did this study take place?

The Sponsor ran this study at 1 location in Belgium.

When did this study take place?

It began 08 November 2021 and ended 27 July 2023.

Who participated in this study?

The study included healthy adult participants who must have been 18 to 60 years of age. Japanese participants must have had 4 biological Japanese grandparents who were born in Japan.

- A total of 119 men participated
- A total of 1 woman participated
- All participants were between the ages of 19 years and 60 years

A total of 120 participants joined the study. Of these, 109 joined Part A of the study and 11 joined Part B of the study.

Of the 109 participants who started Part A of the study, 104 finished the study. Five did not finish Part A of the study because of medical problems that occurred during the study.

Of the 11 participants who started Part B of the study, 9 finished the study. Two did not finish Part B of the study because of medical problems that occurred during the study.

No participant left before the study was over by their choice.

How long did the study last?

Study participants were in the study for about 11 weeks. The entire study took about 1 year and 8 months to complete. The study was completed as planned.

When the study ended in July 2023, the Sponsor began reviewing the information collected. The Sponsor then created a report of the results. This is a summary of that report.

What were the results of the study?

Part A of the Study

How did participants feel and what medical problems did they have after taking PF-07258669?

To answer this question, researchers recorded the medical problems that participants had during the study (described later in this report), clinical laboratory tests, vital signs (blood pressure and heart rate), electrical activity of the heart, and suicide risk.

Clinical Laboratory Tests

Researchers measured laboratory tests in participants during the study to see if they changed during treatment. These tests looked at things like liver function, white blood cells, kidney function, and fat levels in the blood.

A total of 26 out of 29 (89.7%) participants who received placebo and 61 out of 80 (76.3%) participants who received a dose of PF-07258669 had abnormal laboratory tests.

Vital Signs

Researchers measured vital signs (heart rate and blood pressure) during the study to see if they changed during treatment. Overall, researchers found that changes in vital signs were similar for participants who received placebo and participants who received PF-07258669.

Electrical Activity of the Heart

Heart electrical activity was recorded by using an electrocardiogram (or "ECG"). By measuring the electrical activity of the heart, researchers can learn more about how it is functioning.

Four out of 109 (3.7%) participants in Part A of the study had an abnormal ECG recording. All of these participants received PF-07258669. No participants who received placebo had an abnormal ECG recording.

Suicide Risk

Suicide risk was measured by giving participants a questionnaire called the Columbia Suicide Severity Rating Scale. Based on responses to the questionnaire, no participants in the study developed an increase in suicide risk.

Part B of the Study

How did PF-07258669 affect midazolam levels in the body?

To test this, researchers measured the amount of midazolam in the blood after participants took midazolam alone, midazolam + 180 mg PF-07258669 on Day 2, and midazolam + 180 mg PF-07258669 on Day 10.

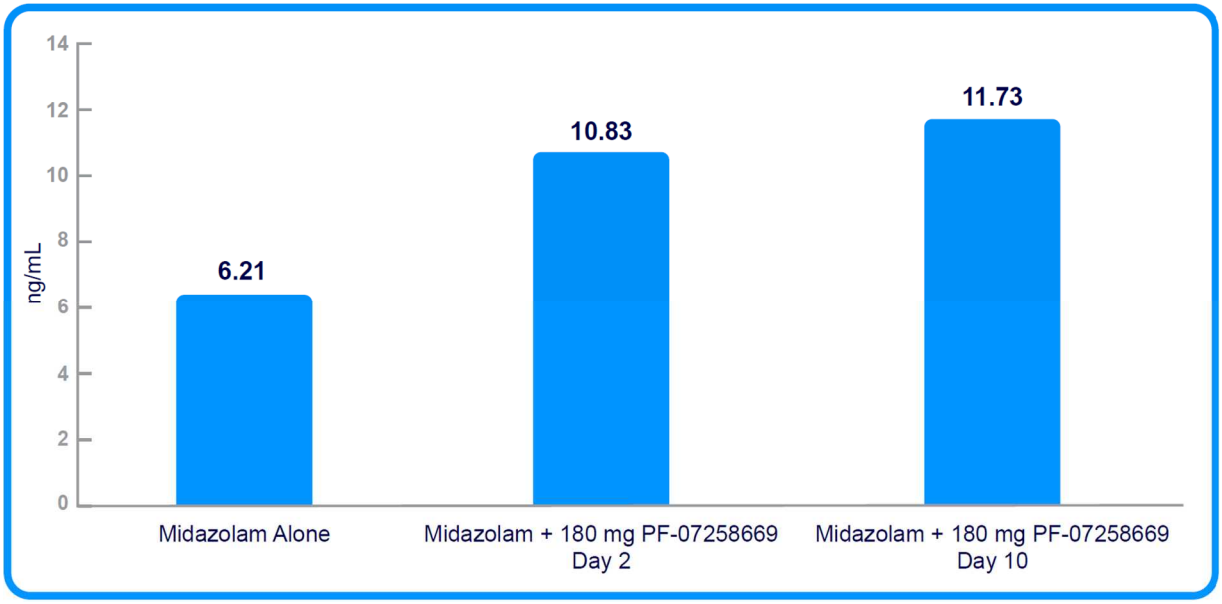
What was the amount of midazolam in the blood after participants took midazolam alone or in combination with 180 mg PF-07258669?

- The highest amount of midazolam in the blood when midazolam was taken alone was 6.21 nanogram per milliliter, also called ng/mL. The ng/mL is a unit to measure the amount of drug in the blood. This is shown in Figure 3.
- The highest amount of midazolam in the blood when midazolam + 180 mg PF-07258669 was taken on Day 2 was 10.83 ng/mL. This is shown in Figure 3.

- The highest amount of midazolam in the blood when midazolam + 180 mg PF-07258669 was taken on Day 10 was 11.73 ng/mL. This is shown in Figure 3.

- Researchers determined that PF-07258669 increased midazolam levels in the blood.

Figure 3. Highest Level of Midazolam in the Blood When Taken Alone or With 180 mg PF-07258669



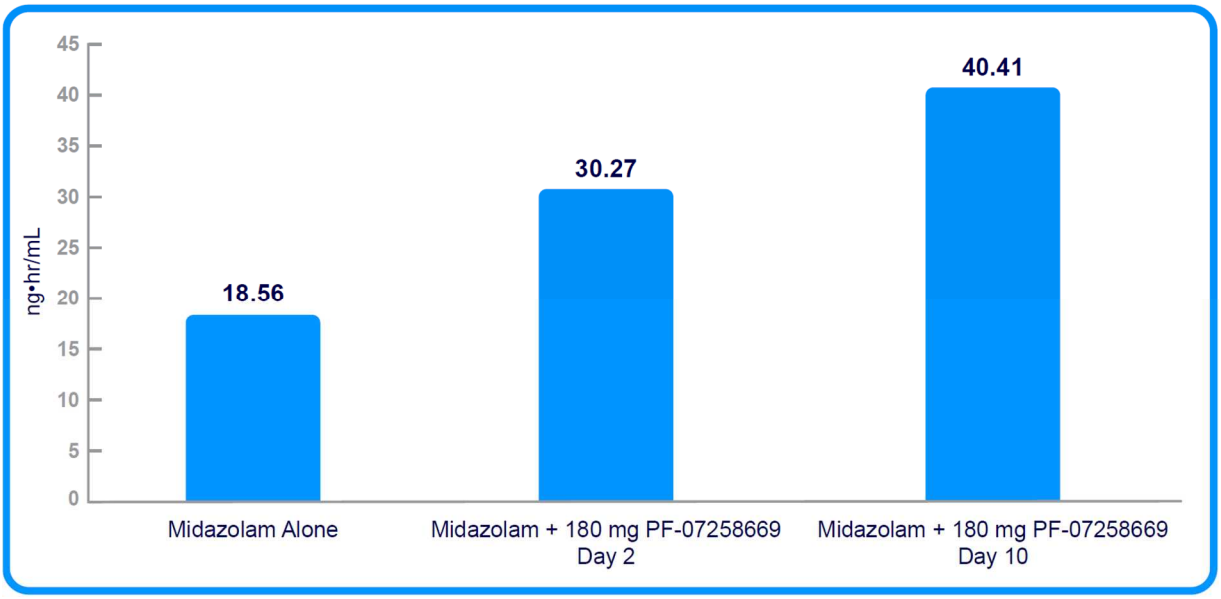
- The amount of midazolam in the blood from when midazolam alone was taken to the time when midazolam was last detected in the blood was 18.56 nanogram hours per milliliter, also called ng•hr/mL. The ng•hr/mL is a unit used to measure total amount of drug over time in the blood. This is shown in Figure 4.

- The amount of midazolam in the blood from when midazolam + 180 mg PF-07258669 was taken on Day 2 to the time

when midazolam was last detected in the blood was 30.27 ng•hr/mL. This is shown in Figure 4.

- The amount of midazolam in the blood from when midazolam + 180 mg PF-07258669 was taken on Day 10 to the time when midazolam was last detected in the blood was 40.41 ng•hr/mL. This is shown in Figure 4.
- Researchers determined that PF-07258669 increased the amount of midazolam in the blood from when midazolam was taken to when midazolam was last detected in the blood.

Figure 4. Amount of Midazolam in the Blood From When it Was Taken (Alone or With PF-07258669) to When it Was Last Detected in the Blood



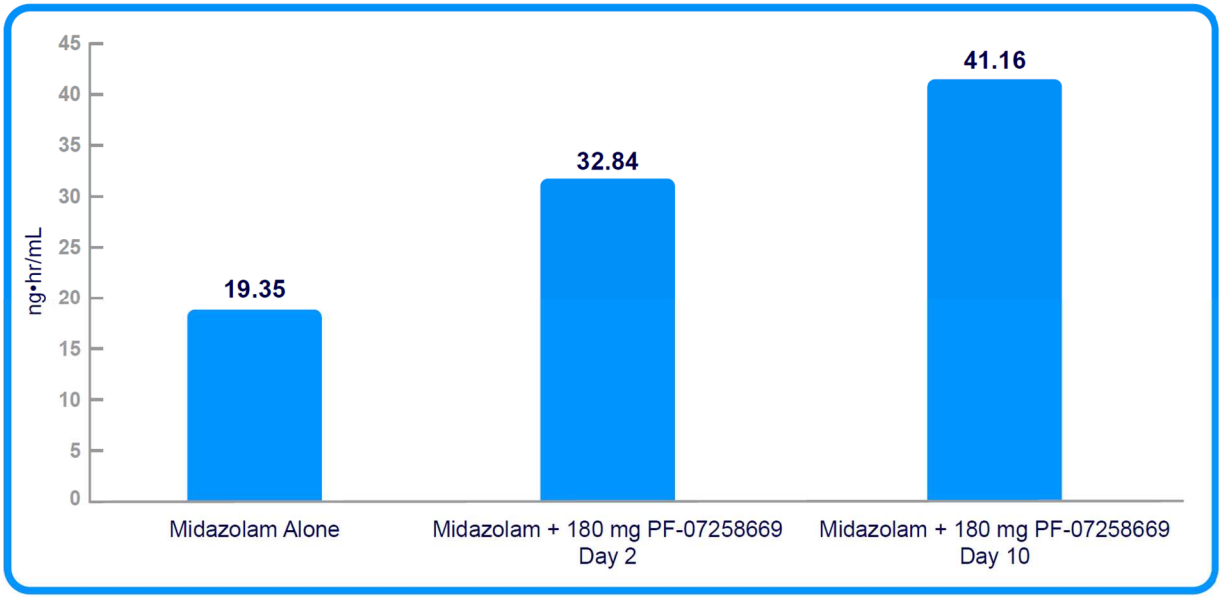
- The estimated total amount of midazolam in the blood from when midazolam alone was taken until midazolam was removed from the body was 19.35 ng•hr/mL. This is shown in Figure 5.

- The estimated total amount of midazolam in the blood from when midazolam + 180 mg PF-07258669 was taken on Day 2 until midazolam was removed from the body was 32.84 ng•hr/mL. This is shown in Figure 5.

- The estimated total amount of midazolam in the blood from when midazolam + 180 mg PF-07258669 was taken on Day 10 until midazolam was removed from the body was 41.16 ng•hr/mL. This is shown in Figure 5.

- Researchers determined that PF-07258669 increased the amount of midazolam in the blood from when midazolam was taken to when midazolam was removed from the body.

Figure 5. Estimated Total Amount of Midazolam in the Blood From When it Was Taken (Alone or With PF-07258669) Until it Was Removed From the Body



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 unknown 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.

In Part A, 87 out of 109 (79.8%) participants had at least 1 medical problem. A total of 5 participants left the study because of medical problems. The most common medical problems – those reported by more than 10.0% of total participants – are described below.

Below are instructions on how to read Table 1. These instructions also apply for Tables 2, 3, 4, and 5.

Instructions for Understanding Table 1.

- The **1st** column of Table 1 lists medical problems that were commonly reported by participants on the high carbohydrate-high calorie diet in Part A of the study. All

medical problems reported by more than 10.0% of total participants on this diet are listed.

- The **2nd** column tells how many of the 6 participants taking placebo on the high carbohydrate-high calorie diet reported each medical problem. Below this number is the percentage of the 6 participants taking placebo on the high carbohydrate-high calorie diet who reported the medical problem.
- The **3rd** column tells how many of the 8 participants taking PF-07258669 2 mg on the high carbohydrate-high calorie diet reported each medical problem. Below this number is the percentage of the 8 participants taking PF-07258669 2 mg on the high carbohydrate-high calorie diet who reported the medical problem.
- The **4th** column tells how many of the 8 participants taking PF-07258669 3 mg on the high carbohydrate-high calorie diet reported each medical problem. Below this number is the percentage of the 8 participants taking PF-07258669 3 mg on the high carbohydrate-high calorie diet who reported the medical problem.
- The **5th** column tells how many of the 7 participants taking PF-07258669 6 mg on the high carbohydrate-high calorie diet reported each medical problem. Below this number is the percentage of the 7 participants taking PF-07258669 6 mg on the high carbohydrate-high calorie diet who reported the medical problem.
- Using these instructions, you can see that:

- 3 out of 6 (50.0%) participants taking the placebo reported feeling tired.
- 3 out of 8 (37.5%) participants taking PF-07258669 2 mg reported feeling tired.
- 0 out of 8 (0%) participants taking PF-07258669 3 mg reported feeling tired.
- 0 out of 7 (0%) participants taking PF-07258669 6 mg reported feeling tired.

Table 1. Part A: Commonly reported medical problems by study participants on the high carbohydrate-high calorie diet

Medical Problem	Placebo (6 Participants)	PF-07258669 2 mg (8 Participants)	PF-07258669 3 mg (8 Participants)	PF-07258669 6 mg (7 Participants)
Feeling tired	3 out of 6 participants (50.0%)	3 out of 8 participants (37.5%)	0	0
Irritation on the body where the medicine was given	0	1 out of 8 participants (12.5%)	0	2 out of 7 participants (28.6%)

Table 1. Part A: Commonly reported medical problems by study participants on the high carbohydrate-high calorie diet

Medical Problem	Placebo (6 Participants)	PF-07258669 2 mg (8 Participants)	PF-07258669 3 mg (8 Participants)	PF-07258669 6 mg (7 Participants)
Flat, raised red skin rash	1 out of 6 participants (16.7%)	2 out of 8 participants (25.0%)	0	0
Upset stomach	2 out of 6 participants (33.3%)	0	0	1 out of 7 participants (14.3%)
Headache	1 out of 6 participants (16.7%)	0	1 out of 8 participants (12.5%)	1 out of 7 participants (14.3%)
Stiffness in muscles, joints, and bones	2 out of 6 participants (33.3%)	1 out of 8 participants (12.5%)	0	0

Table 2. Part A: Commonly reported medical problems by study participants on the standard diet

Medical Problem	Placebo (10 Participants)	PF-07258669 6 mg (8 Participants)	PF-07258669 20 mg (8 Participants)	PF-07258669 60 mg (8 Participants)	PF-07258669 125 mg (8 Participants)	PF-07258669 180 mg (8 Participants)
Feeling hungry	1 out of 10 participants (10.0%)	0	1 out of 8 participants (12.5%)	4 out of 8 participants (50.0%)	0	0
Dry skin	2 out of 10 participants (20.0%)	1 out of 8 participants (12.5%)	0	0	4 out of 8 participants (50.0%)	0

Table 3. Part A: Commonly reported medical problems by study participants on the high fat-high calorie diet

Medical Problem	Placebo (12 Participants)	PF-07258669 180 mg (12 Participants)
Dry skin	1 out of 12 participants (8.3%)	3 out of 12 participants (25.0%)

Table 4. Part A: Commonly reported medical problems by Japanese study participants on the standard diet		
Medical Problem	**Placebo (1 Participant)**	**PF-07258669 180 mg (5 Participants)**
Small tear in the lining of the anus	0	1 out of 5 participants (20.0%)
Gas	0	1 out of 5 participants (20.0%)
Dizziness when changing posture	0	1 out of 5 participants (20.0%)
Sleepiness	0	1 out of 5 participants (20.0%)
Feeling hungry	0	1 out of 5 participants (20.0%)

In Part B, 8 out of 11 (72.7%) participants had at least 1 medical problem. A total of 2 participants left the study because of medical problems. The most common medical problems – those reported by more than 10.0% of total participants – are described below.

Table 5. Part B: Commonly reported medical problems by study participants in Part B of the study			
Medical Problem	Midazolam Single Dose (11 Participants)	PF-07258669 180 mg + Midazolam on Day 2 (11 Participants)	PF-07258669 180 mg + Midazolam on Day 10 (9 Participants)
Feeling hungry	0	2 out of 11 participants (18.2%)	0
ALT liver test increased	0	2 out of 11 participants (18.2%)	0
Collection of blood under the skin	1 out of 11 participants (9.1%)	1 out of 11 participants (9.1%)	0

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.

In Part A of the study, 1 participant (0.9%, or 1 out of 109 participants) had a serious medical problem.

- This participant was in the high carbohydrate-high calorie diet group who took a PF-07258669 dose level of 3 mg every 8 hours. They had a serious medical problem of “signs and symptoms of a

nervous system disorder". Researchers do not believe that this serious medical problem was related to the study medication.

In Part B of the study, no participant had a serious medical problem.

No participants died during the study.

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:

www.pfizer.com/research/research_clinical_trials/trial_results	Use the protocol number C4541003

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

www.clinicaltrials.gov	Use the study identifier **NCT05113940**
www.clinicaltrialsregister.eu	Use the study identifier 2021-004037-36

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!