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:	Nirmatrelvir (PF-07321332)
Protocol Number:	C4671013
Dates of Study:	17 September 2021 to 09 December 2021
Title of this Study:	Study to Estimate the Effect of Nirmatrelvir (PF-07321332) in Combination with Ritonavir and Ritonavir Alone on the Level of Midazolam in the Blood of Healthy Participants COVID-19: A Phase 1, Open-Label, 3-Treatment, 6-Sequence, 3-Period Crossover Study to Estimate the Effect of PF-07321332/Ritonavir and Ritonavir on the Pharmacokinetics of Midazolam in Healthy Participants
Date(s) of this Report:	20 April 2022

– 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 COVID-19?

In December 2019, Coronavirus disease 2019 (COVID-19) was identified as a new, potentially deadly, respiratory infection caused by the new coronavirus, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The World Health Organization (WHO) declared COVID-19 a Public Health Emergency of International Concern (PHEIC) on 20 January 2020 and further described the disease outbreak as a pandemic on 11 March 2020.

SARS-CoV-2 needs an enzyme called "main protease enzyme" (also known as "3CL protease") to replicate (multiply). An enzyme is a protein molecule in cells which enables different biological reactions to happen. Enzymes speed up chemical reactions in the body, but do not get used up in the process; therefore, enzymes can be used repeatedly. If the activity of this enzyme is inhibited, or stopped, the SARS-CoV-2 virus stops replicating.

What is nirmatrelvir, ritonavir, and midazolam?

Participants in this study received 3 different medications: 1) nirmatrelvir/ritonavir combination, 2) ritonavir, and 3) midazolam.

Nirmatrelvir (PF-07321332) is a new oral medicine developed by the researchers for the treatment of SARS-CoV-2 infection. It works by inhibiting the main protease enzyme which the virus needs to replicate.

For the treatment of COVID-19, nirmatrelvir is given with a low dose of another drug called ritonavir. Ritonavir helps to slow the metabolism or breakdown of nirmatrelvir for it to remain active in the body for longer periods of time. It does this by inhibiting the main enzyme that breaks down nirmatrelvir called CYP3A4. Higher levels make nirmatrelvir a more effective treatment against COVID-19. Ritonavir (on its own) is not used to treat the SARS-CoV-2 infection and it is not effective against the virus.

Nirmatrelvir is administered together with ritonavir and is approved to be used for 5 days for patients with mild to moderate COVID-19 at high risk for progression to severe COVID-19.

In this report nirmatrelvir given **together** with ritonavir, is written as "nirmatrelvir/ritonavir".

The third medication given in this study was midazolam. Midazolam is also metabolized (broken down) by the CYP3A4 enzyme (similar to nirmatrelvir). This means that administration of midazolam together with nirmatrelvir and ritonavir could also increase midazolam levels in the blood which could increase the therapeutic effects of midazolam. A higher level of midazolam in the blood could also potentially cause more medical problems due to this medication.

What was the purpose of this study?

The main purpose of this study was to compare the effect of the nirmatrelvir/ritonavir combination, and ritonavir alone, on the levels of midazolam in the blood of participants. This information could help researchers decide on the best way to give nirmatrelvir/ritonavir together with other types of medications in the future, to people who have COVID-19.

This study did not test if nirmatrelvir and/or ritonavir helps to improve COVID-19.

Researchers wanted to know:

- **How did nirmatrelvir/ritonavir and ritonavir alone affect the levels of midazolam in the blood of participants?**
- **What medical problems did participants have during the study?**

What happened during the study?

How was the study done?

This was an "open-label" study, which means that the researchers and the participants knew what study medications the participants were receiving.

Before being included in the study, participants were "screened" to see if they qualify to be in the study. Researchers checked they were healthy and had a negative COVID-19 test.

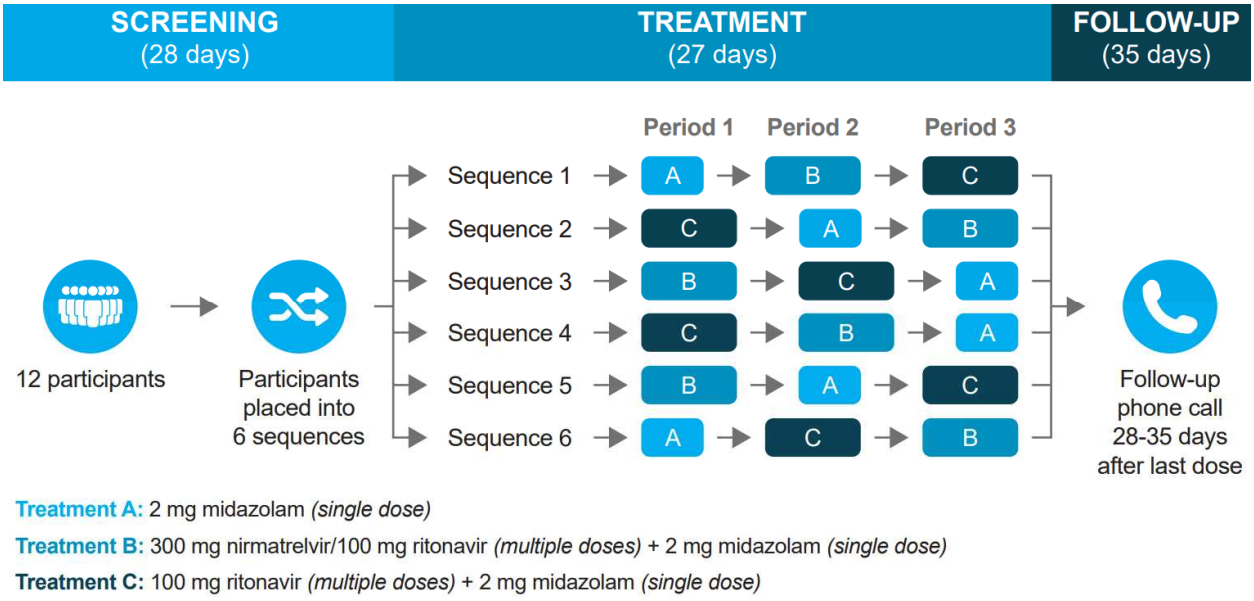
Participants received the nirmatrelvir/ritonavir combination followed by midazolam in 1 period, ritonavir alone followed by midazolam in 1 period, and midazolam alone in 1 period, across 3 different treatment periods. In each period, the medications were given in different orders or "sequences" as shown in **Figure 1**. This means all participants received the same medications, but in a different order according to the sequence they were assigned to. Participants stayed in the study clinic for all 3 treatment periods (28 days and 27 nights).

Study medications shown in **Figure 1** were as follows:

- Treatment A = participants received a single oral dose of 2 mg midazolam on Day 1 of this period, followed by 2 days of no dosing, called a "washout period" (Treatment A period duration: 3 days).
- Treatment B = participants received 300 mg nirmatrelvir/100 mg ritonavir every 12 hours for 9 doses; that is from the morning of Day 1 to the morning of Day 5 of this period. On the morning of Day 5, participants also received a single oral dose of 2 mg midazolam, followed by a 7-day washout period. (Treatment B period duration: 12 days).
- Treatment C = participants received 100 mg ritonavir alone every 12 hours for 9 doses; that is from the morning of Day 1 to the morning of Day 5 of this period. On the morning of Day 5, participants also received a single oral dose

of 2 mg midazolam, followed by a 7-day washout period. (Treatment C period duration: 12 days).

Figure 1. Study Plan



Researchers took samples of blood from participants during the study and measured the amount of midazolam when it was given alone, and when it was given with nirmatrelvir/ritonavir or ritonavir alone. Researchers also checked the participants' health during the study and asked them how they were feeling.

Participants received a follow-up phone call from researchers 28-35 days after they received their last dose of study medication, to see how they were feeling.

Researchers then compared the results of participants taking different sequence of the study medications.

Where did this study take place?

The Sponsor ran this study at 1 location in Belgium.

When did this study take place?

It began 17 September 2021 and ended 09 December 2021.

Who participated in this study?

The study included 12 healthy participants who met the inclusion/exclusion criteria for things such as age and health status.

- A total of 11 men participated
- 1 woman participated
- All participants were between the ages of 21 and 50 years

Of the 12 participants who started the study, 10 participants finished all 6 treatment sequences. Two participants did not complete all 6 treatment sequences and were discontinued from the study because of medical problems.

How long did the study last?

Study participants were in the study for up to 13 weeks. The entire study took about 3 months to complete.

When the study ended in December 2021, 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?

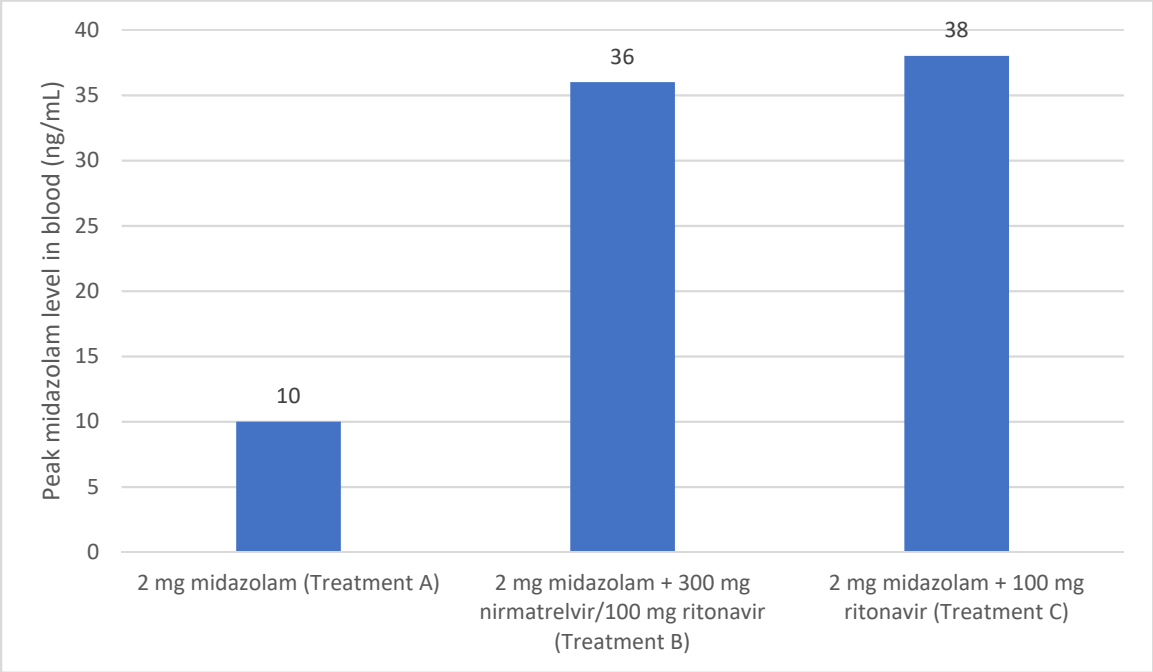
How did nirmatrelvir/ritonavir and ritonavir alone affect the levels of midazolam in the blood of participants?

The study found administration of midazolam with nirmatrelvir/ritonavir or ritonavir increased the level of midazolam in the blood of participants.

What was the amount of midazolam in the blood after participants took 2 mg of midazolam with 300 mg nirmatrelvir/100 mg ritonavir and 100 mg ritonavir alone in different sequences?

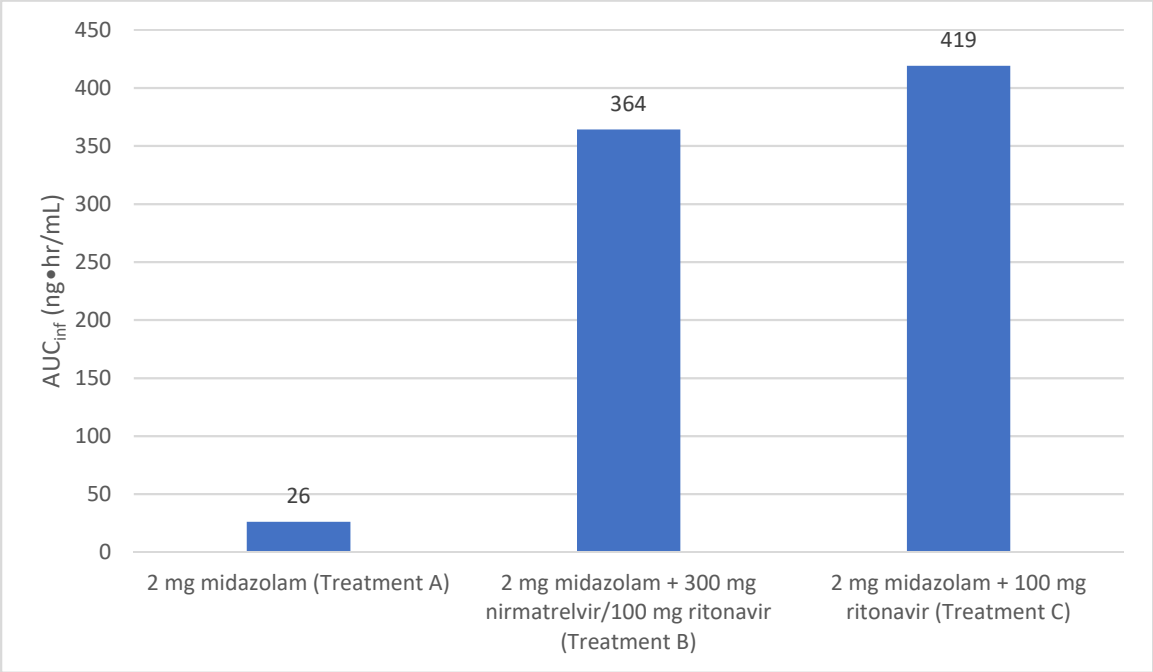
- The highest (peak) amount of midazolam in the blood after participants took midazolam alone (Treatment A), and midazolam with multiple doses of 300 mg nirmatrelvir/100 mg ritonavir (Treatment B) or with multiple doses of 100 mg ritonavir (Treatment C) is shown in **Figure 2**. The amount of midazolam in the blood was measured in nanograms per milliliter, also called ng/mL.
- The study found that the peak amount of midazolam in the blood was noticeably higher when it was given with either; multiple doses of 300 mg nirmatrelvir/100 mg ritonavir or with multiple doses of 100 mg ritonavir, compared to when it was given alone.
- The peak amount of midazolam in the blood was about the same when it was given with multiple doses of 300 mg nirmatrelvir/100 mg ritonavir compared to when it was given with multiple doses of 100 mg ritonavir.

Figure 2. The peak level of midazolam in the blood of participants



- The estimated total amount of midazolam from when midazolam was taken until midazolam was removed from the body (known as AUC_{inf}) is shown in **Figure 3** for each treatment group and was measured in 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.
- The study found that participants had 12 times higher AUC_{inf} values for midazolam, when it was given with multiple doses of 300 mg nirmatrelvir/100 mg ritonavir or with multiple doses of 100 mg ritonavir, compared to when it was given alone. This means that their bodies were exposed to midazolam for a longer time when it was taken with nirmatrelvir/ritonavir or ritonavir alone, than when midazolam was taken on its own.
- The total AUC_{inf} values for midazolam in the blood was slightly lower when it was given with multiple doses of 300 mg nirmatrelvir/100 mg ritonavir compared to when it was given with multiple doses of 100 mg ritonavir.

Figure 3. AUC_{inf} of midazolam



Based on these results, the researchers have decided that the results are not likely the result of chance. 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.

At least 1 medical problem each was reported for:

- 4 participants (40%) who received midazolam 2 mg,
- 9 participants (82%) who received 300 mg nirmatrelvir/100 mg ritonavir + midazolam 2 mg, and
- 7 participants (64%) who received 100 mg ritonavir + midazolam 2 mg.

A total of 2 participants left the study because of medical problems. The most common medical problems – those reported by 2 or more participants in any treatment period – are described below.

Below are instructions on how to read Table 1.

Instructions for Understanding Table 1.

- The **1st** column of Table 1 lists medical problems that were commonly reported during the study. All medical problems reported by 2 or more participants in any treatment period are listed.
- The **2nd** column tells how many of the 10 participants who received 2 mg midazolam alone reported each medical problem. Next to this number is the percentage of the 10 participants who received 2 mg midazolam alone who reported the medical problem.
- The **3rd** column tells how many of the 11 participants who received multiple doses of 300 mg nirmatrelvir/100 mg ritonavir + a single dose of 2 mg midazolam who reported each medical problem. Next to this number is the percentage of the 11 participants who received 300 mg nirmatrelvir/100 mg ritonavir + 2 mg midazolam who reported the medical problem.
- The **4th** column tells how many of the 11 participants who received multiple doses of 100 mg ritonavir + a single dose of 2 mg midazolam who reported each medical problem. Next to this number is the percentage of the 11 participants who received 100 mg ritonavir + 2 mg midazolam who reported the medical problem.
- Using these instructions, you can see that 6 out of the 11 participants (54%) who received 300 mg nirmatrelvir/100 mg ritonavir + 2 mg midazolam and 1 out of the 11 participants who received 100 mg ritonavir + 2 mg midazolam reported 'bad taste in mouth'.

Table 1. Commonly reported medical problems reported by 2 or more study participants in any treatment period			
Medical Problem	**Midazolam 2 mg (10 Participants)**	**Nirmatrelvir 300 mg/ ritonavir 100 mg + Midazolam 2 mg (11 Participants)**	**Ritonavir 100 mg + Midazolam 2 mg (11 Participants)**
Bad taste in mouth	0 out of 10 participants (0%)	6 out of 11 participants (54%)	1 out of 11 participants (9%)
Sleepiness	1 out of 10 participants (10%)	3 out of 11 participants (27%)	3 out of 11 participants (27%)

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. No participants in this study 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.clinicaltrials.gov Use the study identifier **NCT05032950**

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!