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:	Nirmatrelvir (PF-07321332)
Protocol Number:	C4671011
Dates of Study:	15 June 2021 to 07 October 2021
Title of this Study:	A Study to Assess the Pharmacokinetics, Safety and Tolerability of PF-07321332 Combined with Ritonavir in Adult Participants With Renal Impairment and in Healthy Participants With Normal Renal Function [A Phase 1, Non-Randomized, Open-Label Study to Assess the Pharmacokinetics, Safety and Tolerability of PF-07321332 Boosted With Ritonavir in Adult Participants With Renal Impairment and in Healthy Participants With Normal Renal Function]
Date(s) of this Report:	25 May 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 a main protease enzyme also known as 3CL protease to replicate or reproduce. An enzyme is a protein molecule in cells which works as a biological promoter to facilitate biological reactions. 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. Medications known as main protease enzymes or 3CL inhibitors can be used as treatments for COVID-19 infections.

What is nirmatrelvir?

Nirmatrelvir is an effective inhibitor of the SARS-CoV-2 main protease enzyme and has been shown to have the potential to be used as a treatment for SARS-CoV-2 infections. Co-administration with a low dose of ritonavir helps slow the metabolism, or breakdown, of nirmatrelvir for it to remain active in the body for longer periods of time. Higher levels make nirmatrelvir a more effective treatment against COVID-19. Ritonavir is not used to treat the SARS-CoV-2 virus and it is not effective against the virus.

Nirmatrelvir is administered in combination with ritonavir and is authorized to be used for 5 days for patients with mild to moderate COVID-19 at high risk for progression to severe COVID-19 and some patients may have some level of impaired or decreased kidney function. Impaired kidney function is when your kidneys are not working as well as they should. Nirmatrelvir, when given with ritonavir, is eliminated from the body by the kidneys and ritonavir is not eliminated by the kidneys.

What was the purpose of this study?

The purpose of this study was to learn how nirmatrelvir boosted with ritonavir moved through the body and how long it stayed in the body in participants with normal kidney function, and participants with mild, moderate, or severe kidney impairment to develop dosing recommendations for COVID-19 infected participants with kidney disease. After nirmatrelvir and ritonavir are swallowed and absorbed, nirmatrelvir and ritonavir enter the bloodstream and the body organs (for example, stomach, liver, and kidneys). Afterwards, nirmatrelvir is removed from the body through urine and ritonavir is removed from the body through feces.

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

Researchers wanted to know:

- **How did nirmatrelvir and ritonavir move and act in the body?**
- **What medical problems did participants have during the study?**

What happened during the study?

How was the study done?

Researchers tested 100 mg of nirmatrelvir in combination with 100 mg of ritonavir on a group of participants (who were not infected with COVID-19) with normal kidney function, and participants with mild, moderate, or severe kidney impairment to learn how nirmatrelvir acted in the body.

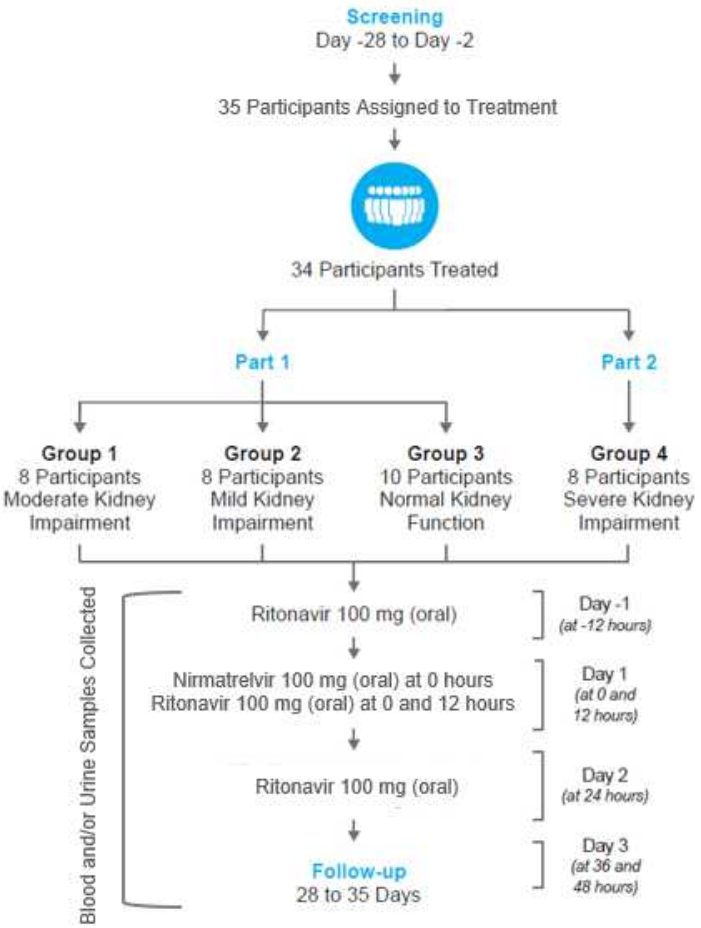
Participants were divided into 4 cohorts or groups depending on the status of their kidney function:

- Group 1: Moderate kidney impairment

- Group 2: Mild kidney impairment
- Group 3: Normal kidney function
- Group 4: Severe kidney impairment

Participants were to take nirmatrelvir at doses of 100 mg and ritonavir at doses of 100 mg. Researchers took samples of blood and urine from participants during the study and measured the amount of nirmatrelvir and ritonavir. The study design is shown in Figure 1 below.

Figure 1. The study design showing how the study was done



Where did this study take place?

The Sponsor ran this study at 4 locations in the United States in North America.

When did this study take place?

It began 15 June 2021 and ended 07 October 2021.

Who participated in this study?

The study included healthy participants and participants with mild, moderate, or severe kidney impairment who met the inclusion criteria for things such as: men or women between the ages of 18 and 75 years, general good health, have normal kidney function or impaired kidney function.

- A total of 23 men participated
- A total of 11 women participated
- All participants were between the ages of 47 and 76 years

Of the 34 participants who were given treatment, 33 participants completed the study. One participant in the severe kidney impairment group did not finish the study because:

- They experienced a medical problem after they received the last dose of nirmatrelvir and ritonavir.

How long did the study last?

Study participants were in the study for approximately 5 weeks. The entire study took 4 months to complete.

When the study ended in October 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?

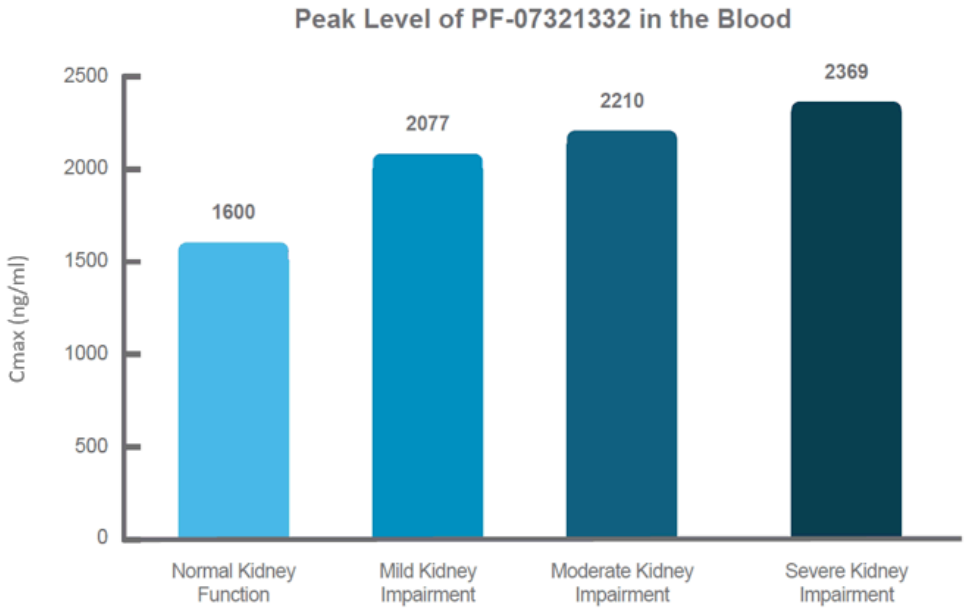
How did nirmatrelvir and ritonavir move and act in the body?

The study was done to see how nirmatrelvir boosted with ritonavir entered and moved through the body and how long it stayed in the body. Researchers used different factors to measure how nirmatrelvir entered and moved through the body and how long it stayed in the body. These factors are shown below.

What was the amount of nirmatrelvir in the blood after participants took 100 mg of nirmatrelvir?

- The highest amount of nirmatrelvir in the blood after participants took 100 mg of nirmatrelvir (known as C_{max}) is shown in Figure 2. The amount of drug in the blood was measured in nanograms per milliliter, also called ng/mL. The C_{max} values increased for the mild, moderate, and severe kidney impairment groups when compared to the normal kidney function group.

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



- The kidney clearance (CLr) is the volume of blood, in liters (L), that has had nirmatrelvir removed every hour (hr). This was measured in L/hr. Researchers noticed a decrease in CLr especially for the moderate and severe kidney impairment groups.
    - Normal kidney function: 2 L/hr
    - Mild kidney impairment: 2 L/hr
    - Moderate kidney impairment: 1 L/hr
    - Severe kidney impairment: 0.4 L/hr
- The estimated total amount of nirmatrelvir from when nirmatrelvir was taken until nirmatrelvir was removed from the body (known as AUC_{inf}) is shown below 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.
    - Participants with moderate and severe kidney impairment had higher AUC_{inf} values which meant that their bodies were exposed to nirmatrelvir for longer than those with normal kidney function and mild kidney impairment.
        - Normal kidney function: 14460 ng.hr/mL
        - Mild kidney impairment: 17910 ng.hr/mL
        - Moderate kidney impairment: 27110 ng.hr/mL
        - Severe kidney impairment: 44040 ng.hr/mL
- The amount eliminated (Ae) or the amount of nirmatrelvir that left the body (unchanged) in the urine was also determined. Unchanged nirmatrelvir means that it was not broken down by the body. The Ae was measured in milligrams (mg) which is a unit used to measure the amount of nirmatrelvir.
    - Normal kidney function: 31 mg

- Mild kidney impairment: 43 mg
- Moderate kidney impairment: 31 mg
- Severe kidney impairment: 18 mg

How long, in hours, did it take for nirmatrelvir to reach its highest amount in the blood after participants took 100 mg of nirmatrelvir (known as T_{max})?

- Normal kidney function: 2 hours
- Mild kidney impairment: 2 hours
- Moderate kidney impairment: 3 hours
- Severe kidney impairment: 3 hours

How long did it take for nirmatrelvir to be removed from the body after participants took 100 mg of nirmatrelvir?

- The terminal half-life ($t_{½}$) is the number of hours it took for nirmatrelvir to decrease by half in the body after participants took 100 mg of nirmatrelvir and is shown below. The $t_{½}$ for participants with moderate or severe kidney impairment was longer than the $t_{½}$ for participants with normal kidney function or mild kidney impairment.
  - Normal kidney function: 8 hours
  - Mild kidney impairment: 7 hours
  - Moderate kidney impairment: 10 hours
  - Severe kidney impairment: 13 hours

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

Nine out of 34 (26%) participants in this study had at least 1 medical problem. A total of 1 (3%) participants left the study because of medical problems. All medical problems reported by participants 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 participants are listed.
- The **2nd** to **4th** columns tells how many of the 34 participants with normal kidney function, mild, moderate, or severe kidney impairment taking the study medication reported each medical problem. Next to this number is the percentage of the 34 participants taking nirmatrelvir who reported the medical problem.
- Using these instructions, you can see that 2 out of the 8 participants, taking nirmatrelvir in the severe kidney impairment group, reported loss of strength or energy.

Table 1. Commonly reported medical problems by study participants

Medical Problem	Nirmatrelvir (34 Participants)			
	Normal kidney function	Mild kidney impairment	Moderate kidney impairment	Severe kidney impairment
Low red blood cell count	0 out of 10 participants (0%)	0 out of 8 participants (0%)	0 out of 8 participants (0%)	1 out of 8 participants (13%)
Low blood platelets	0 out of 10 participants (0%)	0 out of 8 participants (0%)	0 out of 8 participants (0%)	1 out of 8 participants (13%)
Low heart rate	0 out of 10 participants (0%)	0 out of 8 participants (0%)	0 out of 8 participants (0%)	1 out of 8 participants (13%)
Dry mouth	0 out of 10 participants (0%)	0 out of 8 participants (0%)	0 out of 8 participants (0%)	2 out of 8 participants (25%)
Sensation of wanting to vomit	0 out of 10 participants (0%)	0 out of 8 participants (0%)	0 out of 8 participants (0%)	1 out of 8 participants (13%)
Loss of strength or energy	0 out of 10 participants (0%)	0 out of 8 participants (0%)	0 out of 8 participants (0%)	2 out of 8 participants (25%)
Infection of the lung	0 out of 10 participants (0%)	0 out of 8 participants (0%)	0 out of 8 participants (0%)	1 out of 8 participants (13%)
High blood potassium	0 out of 10 participants (0%)	0 out of 8 participants (0%)	0 out of 8 participants (0%)	1 out of 8 participants (13%)
Low blood sodium	0 out of 10 participants (0%)	0 out of 8 participants (0%)	0 out of 8 participants (0%)	1 out of 8 participants (13%)
Too much acid in the body fluids	0 out of 10 participants (0%)	0 out of 8 participants (0%)	0 out of 8 participants (0%)	1 out of 8 participants (13%)
Disturbance in the sense of taste	0 out of 10 participants (0%)	0 out of 8 participants (0%)	0 out of 8 participants (0%)	2 out of 8 participants (25%)
Headache	2 out of 10 participants (20%)	0 out of 8 participants (0%)	1 out of 8 participants (13%)	0 out of 8 participants (0%)
Uneasy mood	1 out of 10 participants (10%)	0 out of 8 participants (0%)	0 out of 8 participants (0%)	0 out of 8 participants (0%)
Acute kidney injury	0 out of 10 participants (0%)	0 out of 8 participants (0%)	0 out of 8 participants (0%)	1 out of 8 participants (13%)
Fluid in the lungs	0 out of 10 participants (0%)	0 out of 8 participants (0%)	0 out of 8 participants (0%)	1 out of 8 participants (13%)
Skin irritation	0 out of 10 participants (0%)	1 out of 8 participants (13%)	0 out of 8 participants (0%)	0 out of 8 participants (0%)
Low blood pressure	0 out of 10 participants (0%)	0 out of 8 participants (0%)	0 out of 8 participants (0%)	1 out of 8 participants (13%)

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.

One participant (3%) had serious medical problems.

- One participant in the severe kidney impairment group had fluid in the lungs, acute kidney injury, and infection of the lung.

Researchers do not believe any of the serious medical problems reported by the participant were related to nirmatrelvir.

There were no deaths in this 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:

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

www.clinicaltrials.gov	Use the study identifier NCT04909853
www.pfizer.com/research/research_clinical_trials/trial_results	Use the protocol number C4671011

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!