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)/Ritonavir

Protocol Number: C4671012

Dates of Study: 21 September 2021 to 06 December 2021

Title of this Study: Study the Effect of Nirmatrelvir (PF-07321332)/Ritonavir and Ritonavir alone on Dabigatran in Healthy Participants

[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 Dabigatran in Healthy Participants]

Date(s) of this Report: 16 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 3-chymotrypsin-like (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 are Nirmatrelvir (PF-07321332)/Ritonavir, Ritonavir and Dabigatran?

Nirmatrelvir is an effective inhibitor of the SARS-CoV-2 main protease enzyme and has shown that it has 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.

Dabigatran is an anticoagulant, which means it treats and prevents blood clots. Dabigatran comes in a capsule that is swallowed.

What was the purpose of this study?

The purpose of this study was to estimate the effect of multiple doses of nirmatrelvir/ritonavir and multiple doses of ritonavir on the pharmacokinetics (PK) of a single dose of dabigatran in healthy adult participants. Pharmacokinetics is the study of the way the body breaks down a drug and removes it.

All participants received single doses of dabigatran 3 times during the study. This dose of dabigatran was either taken alone, or after multiple doses of ritonavir alone, or after multiple doses of nirmatrelvir/ritonavir.

After the 75 mg dabigatran capsule was swallowed, dabigatran entered the body and moved through the body. Dabigatran entered the blood and organs (for example, stomach, liver, and kidneys) when it moved through the body. Afterwards, dabigatran was removed from the body through urine and feces.

Researchers wanted to know:

- **How did multiple doses of nirmatrelvir/ritonavir and ritonavir affect how a single dose of dabigatran moved and acted in the body?**
- **What medical problems did participants have during the study?**

What happened during the study?

How was the study done?

Researchers tested different combinations of dabigatran and ritonavir alone or nirmatrelvir/ritonavir in a group of healthy participants to learn how the study medications acted in the body.

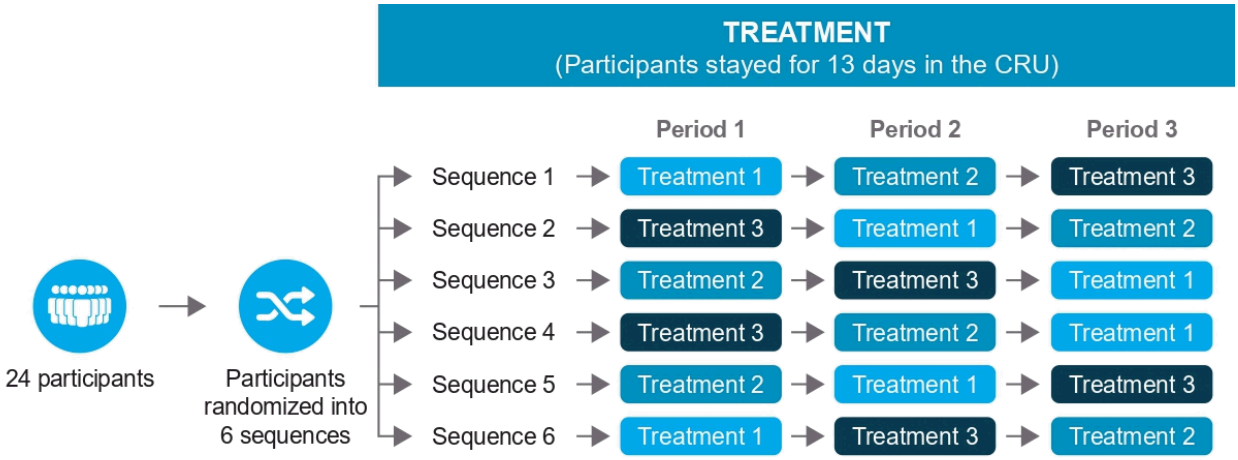
The study consisted of 3 treatments:

- **Treatment 1:** One (1) dose of dabigatran (75 mg) was given.
- **Treatment 2:** Nirmatrelvir 300 mg and ritonavir 100 mg was given every 12 hours for 2 days. On the morning of Day 2, one (1) dose of dabigatran (75 mg) was also given.
- **Treatment 3:** 100 mg of ritonavir was given every 12 hours for 2 days. On the morning of Day 2, one (1) dose of dabigatran (75 mg) was given.

There was a 3-day washout period between each study treatment. A washout is when a participant is not given any other treatment and it gives the body time to eliminate the drug out of their system.

All 24 participants were given Treatments 1, 2 and 3 over the course of 13 days. However, the order in which they received the treatments was different. There were 6 different sequences, with 4 participants in each.

A summary of how the study was done is shown in the below figure:



Treatment 1: One (1) dose of dabigatran (75 mg) was given.

Treatment 2: Nirmatrelvir 300 mg and ritonavir 100 mg was given every 12 hours for 2 days. On the morning of Day 2, one (1) dose of dabigatran (75 mg) was also given.

Treatment 3: Ritonavir 100 mg was given every 12 hours for 2 days. On the morning of Day 2, one (1) dose of dabigatran (75 mg) was given.

Researchers took samples of blood from participants during the study and measured the amount of dabigatran. Researchers also checked the participants' health during the study and asked them how they were feeling.

Researchers then compared the results of participants taking the study medications in different sequences with one another. The participants and researchers knew who took the different treatments at each stage of the study. This is known as an "open label" study.

Participants were assigned to each sequence by chance alone. This is known as a "randomized" study, and it helps make the treatments similar and more even to compare.

Where did this study take place?

The Sponsor ran this study at 1 location in the United States.

When did this study take place?

It began 21 September 2021 and ended 06 December 2021.

Who participated in this study?

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

- A total of 9 men participated
- A total of 15 women participated
- All participants were between the ages of 21 and 60

Of the 24 participants who started the study, 23 finished the study. One (1) participant did not finish the study by choice.

How long did the study last?

Study participants were in the study for 13 days. The entire study took 11 weeks 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.

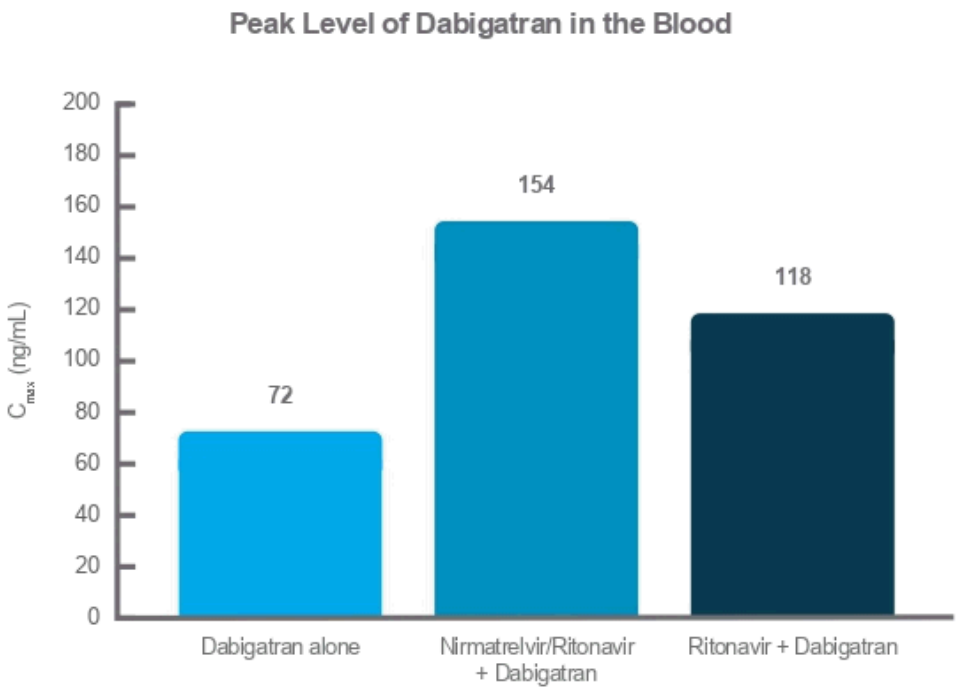
What were the results of the study?

How did multiple doses of nirmatrelvir/ritonavir and ritonavir affect how a single dose of dabigatran moved and acted in the body?

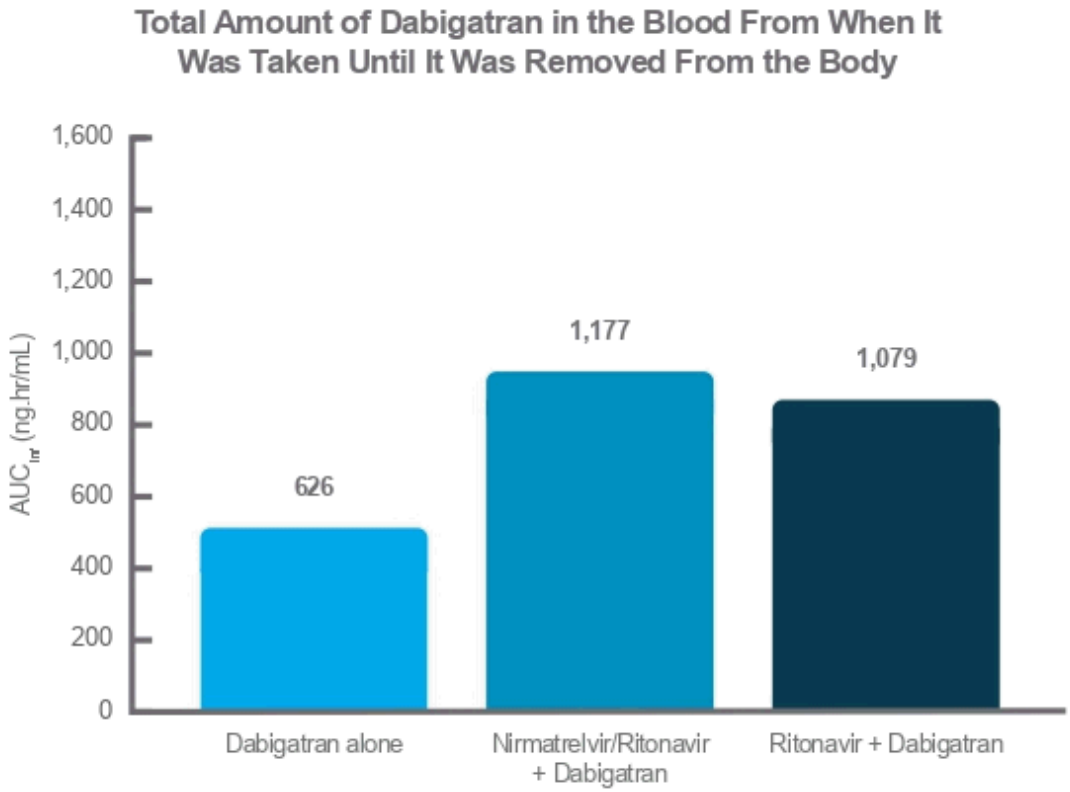
The study was done to see how the order of different treatments affected how dabigatran moves through the body. Researchers used different factors to measure how dabigatran entered and moved through the body and how long it stayed in the body. These factors are shown below.

What was the amount of dabigatran in the blood after participants took 75 mg of dabigatran, and when participants took 75 mg of dabigatran after nirmatrelvir with ritonavir, and when they took 75 mg of dabigatran after ritonavir alone?

- The highest amount of dabigatran in the blood (known as C_{max}) after participants took dabigatran alone or after multiple doses of either nirmatrelvir/ritonavir or after multiple doses of ritonavir is shown in the below figure. The amount of drug in the blood was measured in nanograms per milliliter, also called ng/mL.
- The highest amount of dabigatran in the blood after participants took 75 mg of dabigatran was 72 ng/mL.
- The highest amount of dabigatran in the blood after participants took 75 mg of dabigatran following nirmatrelvir/ritonavir (300 mg of nirmatrelvir and 100 mg of ritonavir)was 154 ng/mL.
- The highest amount of dabigatran in the blood after participants took 75 mg of dabigatran following 100 mg of ritonavir was 118 ng/mL.



- The estimated total amount of dabigatran in the blood, from when dabigatran was taken until it was removed from the body (known as AUC_{inf}) is shown in the below figure for each treatment. This 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 AUC_{inf} after participants took 75 mg of dabigatran was 626 ng.hr/mL.
- The AUC_{inf} after participants took 75 mg of dabigatran following multiple doses of nirmatrelvir/ritonavir (300 mg of nirmatrelvir and 100 mg of ritonavir) was 1177 ng.hr/mL.
- The AUC_{inf} after participants took 75 mg of dabigatran following multiple doses of ritonavir 100 mg was 1079 ng.hr/mL.



To summarize the above results, the concentration of dabigatran in the blood was approximately twice as much when participants took nirmatrelvir/ritonavir or ritonavir before taking dabigatran, compared to taking dabigatran alone.

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

- It took 2 hours for dabigatran to reach its highest amount in the blood after participants took 75 mg of dabigatran.
- It took 2 hours for dabigatran to reach its highest amount in the blood after participants took 75 mg of dabigatran following nirmatrelvir/ritonavir (300 mg of nirmatrelvir and 100 mg of ritonavir).

- It took 2 hours for dabigatran to reach its highest amount in the blood after participants took 75 mg of dabigatran following 100 mg of ritonavir.

How long did it take for dabigatran to be removed from the body after participants took the study treatments?

The terminal half-life ($t_{½}$) is the number of hours it took for dabigatran to decrease by half in the body after participants took the study treatments.

- The $t_{½}$ after participants took 75 mg of dabigatran was 11 hours.
- The $t_{½}$ after participants took 75 mg of dabigatran following nirmatrelvir/ritonavir (300 mg of nirmatrelvir and 100 mg of ritonavir) was 10 hours.
- The $t_{½}$ after participants took 75 mg of dabigatran following 100 mg of ritonavir was 10 hours.

Based on these results, the researchers have decided that the results are not likely the result of chance. Dabigatran may act differently in the body if administered alone or following multiple doses of nirmatrelvir/ritonavir or multiple doses of ritonavir. 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.

Ten (10) out of 24 (38%) participants in this study had at least 1 medical problem. No participants left the study because of medical problems. All the medical problems are described below.

Below are instructions on how to read Table 1.

Instructions for Understanding Table 1.

- The **1st** column of Table 1 lists all the medical problems that were reported during the study.
- The **2nd** column tells how many of the 24 participants taking dabigatran reported each medical problem. Under this number is the percentage of the 24 participants taking this study medication who reported the medical problem.
- The **3rd** column tells how many of the 24 participants taking nirmatrelvir/ritonavir and dabigatran reported each medical problem. Next to this number is the percentage of the 24 participants taking this study medication who reported the medical problem.
- The **4th** column tells how many of the 24 participants taking ritonavir and dabigatran reported each medical problem. Next to this number is the percentage of the 24 participants taking this study medication who reported the medical problem.
- Using these instructions, you can see that 1 out of the 24 (4%) participants taking dabigatran reported indigestion. A total of 0 out of the 24 (0%) participants taking nirmatrelvir/ritonavir and dabigatran reported indigestion, and a total of 0 out of the 24 (0%) participants taking ritonavir and dabigatran reported indigestion.

Table 1. Commonly reported medical problems by study participants			
Medical Problem	Dabigatran (24 Participants)	Nirmatrelvir/ Ritonavir + Dabigatran (24 Participants)	Ritonavir + Dabigatran (24 Participants)
Diarrhea	0 out of 24 participants (0%)	1 out of 24 participants (4%)	0 out of 24 participants (0%)
Indigestion	1 out of 24 participants (4%)	0 out of 24 participants (0%)	0 out of 24 participants (0%)
Common cold	0 out of 24 participants (0%)	1 out of 24 participants (4%)	0 out of 24 participants (0%)
Infection of the kidneys, bladder, or urethra (Urinary tract infections)	1 out of 24 participants (4%)	1 out of 24 participants (4%)	0 out of 24 participants (0%)
Bruising	0 out of 24 participants (0%)	1 out of 24 participants (4%)	0 out of 24 participants (0%)
Back pain	1 out of 24 participants (4%)	0 out of 24 participants (0%)	0 out of 24 participants (0%)
Headache	0 out of 24 participants (0%)	1 out of 24 participants (4%)	2 out of 24 participants (8%)

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 had serious medical problems. 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:

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

www.clinicaltrials.gov Use the study identifier **NCT05064800**

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!