Together, we can explore options that may help improve Long COVID symptoms

RECOVER VITAL

RECOVER
VITAL

Welcome to RECOVER-VITAL

About This Study

RECOVER-VITAL is looking at how study drugs may help adults with Long COVID live with fewer symptoms. Researchers want to learn about the safety and effectiveness of using study drugs for Long COVID, a condition that causes a person to be sick months after getting COVID.

This study includes adults who experience at least 1 of 3 common symptoms:

Autonomic Dysfunction
(dizziness, fast heart rate, shortness of breath, upset stomach, or other changes in body functions that happen automatically)

Cognitive Dysfunction
(trouble thinking clearly or brain fog)

Exercise Intolerance and Fatigue
(exhaustion or low energy that interferes with daily activities)

Why Your Participation Matters

More than 500 million people around the world have had COVID, and it's possible that millions of them could have long-term symptoms. We need more information to support the safe use of potential treatments for people with Long COVID.

With your help, we can better understand why and how Long COVID affects people in different ways and explore possible treatments. This research may help you, your loved ones, and other people with Long COVID.

What to Expect During the Study

Length of Study	Study Visits	Study Drug	Follow-up
Participate in the study for about 6 months	Visit the study clinic at least 4 times	Take the study drug for up to 25 days, provided at no cost	Answer follow-up questions about your health and well-being

What will I do at each visit?
After screening, you will be scheduled to come to the study clinic for several in-person visits. Each visit may last a different amount of time, depending on the study activities you will be asked to complete.

Time estimates are listed below for each in-person visit. Please let the study team know if you have any concerns with the length of the visit and if there is anything that could make your visit more comfortable.

There are 4 required visits to the clinic:
- **Baseline (Day 0) (about 4 hours):** Complete surveys, lab tests (if not done at screening visit), and physical ability and/or brain function tests at the clinic. Enroll in the study and receive your study drug.
- **Study Drug Dosing Midpoint (Day 15) (about 4-6 hours):** Complete surveys and lab tests at the clinic halfway through the study drug dosing period. Receive additional study drug.
- **End of Dosing (Day 25) (about 4-6 hours):** Complete surveys, lab tests, and physical ability and/or brain function tests at the clinic. Return any unused study drug.
- **Follow-Up (Day 90) (about 4 hours):** Complete surveys, lab tests, and physical ability and/or brain function tests at the clinic.

There are also several follow-up points:
- **Follow-Up (Day 45, Day 60, and Day 120):** Complete surveys by phone or online. Complete optional lab tests at the clinic, which will take about 45 minutes.
- **End of Study (Day 180):** Talk to the study team on the phone about your health and well-being. This will take about 30 minutes.

When will the study team check in with me?
You will be asked to complete follow-up surveys:
- about a day after any visit that includes physical ability and/or brain function tests, and
- about once a week from the Baseline visit until the end of the study.

The study team will also do a safety check with you at each study visit and follow-up point.

Why is the study so long if I'm only taking the study drug for a short time?
The information you provide throughout the study is very important to RECOVER research. Follow-up visits and phone calls after you finish taking the study drug help researchers collect more safety information and long-term data on the study drug's effects on your health and well-being.

About the Study Drug: PAXLOVID

Researchers are studying an antiviral drug called PAXLOVID (nirmatrelvir and ritonavir) [packs-LOW-vid (neer-MAT-trel-veer and ruh-TONE-uh-veer)]. PAXLOVID has not been approved by the U.S. Food and Drug Administration (FDA) for treating Long COVID. However, the FDA allows the use of PAXLOVID for the treatment of active COVID-19 infection in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. When a person is given PAXLOVID for an active COVID infection, they usually take the drug for 5 days. In this study, participants will take a study drug for up to 25 days, depending on their study drug assignment.

Researchers believe that viral persistence (when the virus that causes COVID-19 stays in the body and causes damage to organs or the immune system to not function properly) may cause Long COVID symptoms. This study will help us learn if a longer dose of PAXLOVID can help improve these symptoms.

How It Works
PAXLOVID works to stop the virus that causes COVID-19 from multiplying and reduces the amount of it in the body. Each dose of PAXLOVID contains 2 different types of pills:

- **Nirmatrelvir.** This pill is an antiviral drug that helps stop the virus that causes COVID-19 from reproducing in the body.

- **Ritonavir.** This pill helps the levels of nirmatrelvir to last longer in the blood. It works by slowing down the amount of time it takes the body to breakdown the antiviral drug. The dose of ritonavir in this study is not expected to have any effect on the virus that causes COVID-19.

PAXLOVID may interact with other medicines you are taking. The study doctor will talk to you about any concerns. If you start taking a new medicine, please tell your study team.

Side Effects Associated with PAXLOVID

Below are some possible, known side effects associated with PAXLOVID.
There may be unknown risks from participation.

- Altered sense of taste (food tastes funny, bitter, or like metal)
- Diarrhea (loose, watery poop)
- Headache
- High blood pressure
- Abdominal pain (pain in the belly)
- Nausea (feeling sick to the stomach or feeling a need to vomit)
- Vomiting
- Malaise (a feeling of discomfort or illness)

Other possible side effects of PAXLOVID include liver problems and resistance to HIV medicines.

Allergic reactions, including severe allergic reactions (known as "anaphylaxis"), can happen in people taking PAXLOVID.

You should stop taking PAXLOVID and seek immediate medical attention if you experience:

- Serious skin reactions
- Trouble swallowing or breathing
- Swelling of the mouth, lips, or face
- Throat tightness
- Hoarseness of voice

About Your Study Drug Assignment

You will be assigned by chance to one of the following groups:		
PAXLOVID for 25 days	**PAXLOVID for 15 days + Control for 10 days**	**Control for 25 days**

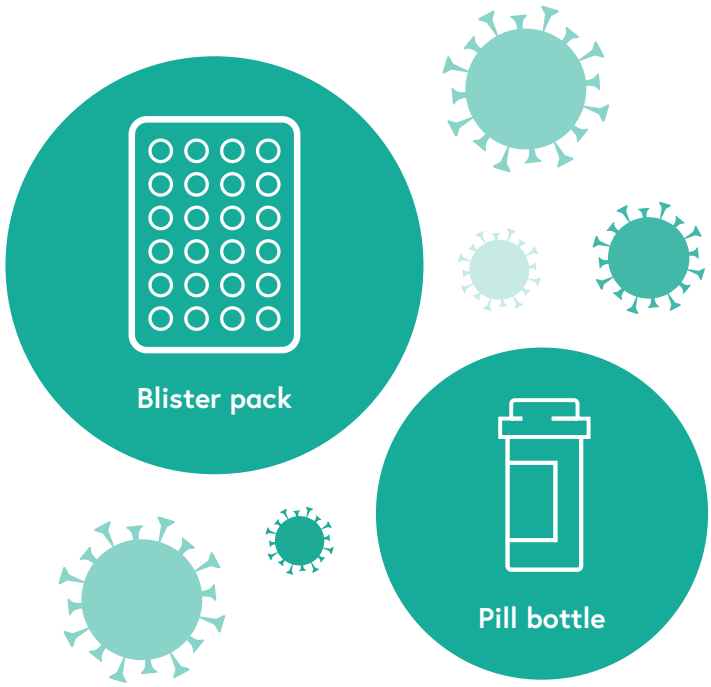
In this study, PAXLOVID and the control are both referred to as study drugs.
- **PAXLOVID** is a combination of nirmatrelvir and ritonavir pills.
- The **control** is a combination of placebo and ritonavir pills. The placebo pill looks like nirmatrelvir but has no active ingredients and should have no effect.

All participants in this study will receive ritonavir. Researchers will use it as a point of comparison so they can learn how different dosing periods of nirmatrelvir affect participants' health. The dose of ritonavir in this study is not expected to have any effect on the virus that causes COVID-19, but ritonavir may cause side effects (see the Side Effects Associated with PAXLOVID section).

You, your study doctor, and the study team will not know which group you are assigned to, but they can quickly find out if there is ever a need to know for your safety or well-being.

What You Will Receive
All participants will receive 2 kits with blister packs and pill bottles. Kit 1 will last 15 days, and Kit 2 will last 10 days.
- Each **blister pack** contains 24 oval, pink pills (6 rows of 4 pills).
- Each **pill bottle** contains 12 oval, white pills.

The blister packs and pill bottles will include extra pills.
- You will need to return any extra pills to the study team at your Dosing Midpoint and End of Dosing visits.



How to Take Your Study Drug

You will take your first dose of the study drug at the clinic. After that, follow the dosing instructions below for your standard or reduced dose. You will take a reduced dose if your kidneys are not fully functioning. Your study doctor will let you know if you need to take a reduced dose.

If You Miss a Dose

If you miss a dose within 8 hours of the time you normally take the pills:
- Take the dose as soon as you remember.
- Take your next dose at the time you normally take the pills.

If you miss a dose by more than 8 hours:
- **Skip the missed dose. Do not double the next dose to make up for a missed dose.**
- Take your next dose at the time you normally take the pills.

If You Take the Wrong Dose
- If you take too much of the study drug, call your healthcare provider or go to the nearest hospital emergency room right away.
- Do not take any more study drug until you have spoken with your study team.

☐ Standard Dose	☐ Reduced Dose
Take 3 pills together (1 from the pill bottle and 2 from the blister pack) twice a day for 25 days.	**Take 2 pills together (1 from the pill bottle and 1 from the blister pack) twice a day for 25 days.**

IMPORTANT REMINDERS

- **Take the pills in your assigned dose together, no more than 15 minutes apart.**
- **Take your assigned dose around the same time each day (in the morning and evening).**
- **Swallow the pills whole. Do not chew, break, or crush the pills.**
- **You can take the pills with or without food.**
- **Many types of medicines can cause a bad taste in your mouth. To help improve your ability to tolerate the study drug, you can take the pills with food, suck on cinnamon-flavored candies or ice, chew gum, or take it with a flavored drink.**

STORING THE STUDY DRUG

- **Store the blister packs and pill bottles at room temperature (between 59°F to 86°F). Keep them away from pets, children, and extreme heat.**
- **Keep the pills in the original blister packs and pill bottles until you are ready to take your dose.**

About the RECOVER Research Biorepository

The RECOVER Research Biorepository is designed to collect and store biospecimens for future research related to the RECOVER Initiative. Biospecimens may include samples of blood, stool (poop), and nasal swabs. These samples will be stored securely until they are used up.

Participating in this study means you agree to share your data and biospecimens with the RECOVER Research Biorepository. **If you choose to participate in this study, your data and samples may also be shared with other researchers for future research, such as developing new tests and treatments for Long COVID or other health problems.** You can change your mind later, but researchers might still use your data and biospecimens if they have already been shared and we are not able to link your samples back to you because they have already been de-identified.

Why is a biorepository needed?
Biospecimens from a blood sample can provide valuable information to researchers. This information is called "biomarkers." For example, a person's blood sugar level is one of the biomarkers for diabetes. Biomarkers can be measured and may provide important information about Long COVID. They may also predict how a patient will respond to a treatment.

How could a biorepository help with Long COVID research?
Sharing your data and biospecimens with the RECOVER Research Biorepository may:

- Increase the possibility of developing new interventions and possible treatments related to Long COVID
- Improve our understanding of how antiviral drugs and other interventions may work to reduce Long COVID symptoms
- Enhance our understanding of how and why Long COVID affects people differently
- Help researchers make important discoveries and uncover possible therapies that could help your family and others in the future

How will my privacy be protected?
Your data and samples will be de-identified, which means they will not include any information that can personally identify you, and researchers cannot easily link your identifying information to the data and samples.

What will the samples be used for?

RECOVER research
The samples will be used for research on COVID and the long-term effects of the virus that causes COVID-19. They may also be used for research on other health problems.

Genetic testing (optional)
The use of your samples for genetic testing is optional, and you can let the study team know your decision in the Informed Consent Form. If you give your permission, researchers may study your genes to look for links to Long COVID. Genetic tests can determine if a person or groups of people are more likely to have certain genetic diseases or conditions. Choosing to say no to genetic testing will not limit your ability to participate in other parts of this study, including using the study interventions.

Will I get any results back from future research use of my data and biospecimens?
No. You should not expect to receive results from any future research that may use your data and biospecimens.

Blood Samples

When will I have blood drawn for the biorepository?
The study team will take about 5 tablespoons (80 ml) of blood from your arm during specified study visits.

Stool Samples

How will I provide stool samples?
After the Baseline and 90-day follow-up visits, you will be asked to provide a stool (poop) sample using an at-home kit. The at-home kit will include a confidential pre-paid box for you to mail your sample directly to the RECOVER Research Biorepository where it will be stored securely.

Why are stool samples important to this research?
People who have had COVID can have changes in their microbiome (microorganisms like fungi, bacteria, and viruses that live in the intestines) in their stool after their infection. Collecting stool samples helps researchers understand changes in the microbiome caused by the COVID-19 infection.

Nasal Swab Samples

Why are nasal swab samples important to this research?
Nasal swab samples help detect the presence of the virus that causes COVID-19 during infection. They will be used to tell researchers information about the study drug, the virus, and your health.

RECOVER-VITAL Participant Schedule

Legend

- Surveys
- Physical Ability Tests
- Brain Function Tests
- Blood
- Nasal Swab
- Stool
- Study Drug
- Safety Check

Study Drug Dosing Period (Day 0 to Day 25)

Day 0	Day 15	Day 25
Baseline Visit (about 4 hours)	**Study Drug Dosing Midpoint Visit (about 4-6 hours)**	**End of Dosing Visit (about 4-6 hours)**
Visit Date:	**Visit Date:**	**Visit Date:**
Information		
• Review current medicines • Review study requirements • Begin study drug • Complete a survey soon after your visit about how you are feeling • Begin weekly surveys by phone or online through the end of the study	• Review current medicines • Check if taking study drug as directed	• Review current medicines • Check if taking study drug as directed • Return any unused study drug • Complete a survey soon after your visit about how you are feeling
Assessments		
• Surveys • Physical ability tests or brain function tests • Blood sample, if needed • Nasal swab samples, if needed • Stool sample, if needed • Safety check	• Surveys • Blood sample • Nasal swab samples • Safety check	• Surveys • Physical ability tests or brain function tests • Blood sample • Nasal swab samples • Safety check

Follow-Up Period (Day 26 to Day 180)

Day 45	Day 60	Day 90	Day 120	Day 180
Follow-Up (about 45 minutes) **Optional Visit Date:**	**Follow-Up (about 45 minutes)** **Optional Visit Date:**	**Follow-Up (about 4 hours)** **Visit Date:**	**Follow-Up (about 45 minutes)** **Optional Visit Date:**	**End of Study Phone Call (about 30 minutes)** **Phone Call Date:**
Information				
• Review current medicines	• Review current medicines	• Review current medicines • Complete a survey soon after your visit about how you are feeling	• Review current medicines	• Review current medicines • End weekly surveys
Assessments				
Required (from home): • Surveys • Safety check **Optional (clinic visit, about 45 minutes):** • Blood sample • Nasal swab samples	**Required (from home):** • Surveys • Safety check **Optional (clinic visit, about 45 minutes):** • Blood sample • Nasal swab samples	• Surveys • Physical ability tests or brain function tests • Blood sample • Nasal swab samples • Stool sample • Safety check	**Required (from home):** • Surveys • Safety check **Optional (clinic visit, about 45 minutes):** • Blood sample • Nasal swab samples	• Surveys • Safety check

If You Become Ill or Injured
Get the medical care that you need right away. Visit your doctor, go to urgent care, or go to the emergency room if needed.

Contact Your Study Team if You
- Receive emergency medical care
- Experience new or worsening symptoms
- Start taking any new medicines
- Change your phone number, email, or home address
- Have questions about the study or the study drug
- Become pregnant

Site Contact Information

RECOVER VITAL

For more information and study updates, visit trials.recovercovid.org/vital

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