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

RECOVER AUTONOMIC

Ivabradine or Placebo Group

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Welcome to RECOVER-AUTONOMIC

About This Study

RECOVER-AUTONOMIC is studying possible treatments to help people with Long COVID live with fewer autonomic dysfunction symptoms. These symptoms are related to nerve damage of the autonomic nervous system, which controls automatic body functions such as heartbeat and blood pressure. Researchers want to learn about the safety and effectiveness of potential treatments for Long COVID, a condition that causes a person to be sick months after getting COVID.

This study will enroll adults who have autonomic dysfunction symptoms when they stand up from sitting or lying down. This condition is known as Postural Orthostatic Tachycardia Syndrome (POTS). Symptoms may include:

Fast Heart Rate

Dizziness

Fatigue

This study will explore whether your symptoms improve from the different potential treatments being studied. The information in this brochure describes what people in the **ivabradine or placebo group** can expect as part of the RECOVER-AUTONOMIC trial.

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.

When final study results become available, a summary will be posted on the study website.

What to Expect in the Ivabradine or Placebo Group

Length of Participation	Study Clinic Visits	Study Drug
Participate in the study for about 6 months, including a 3-month treatment period and a follow-up visit 3 months later	Visit a study clinic 4 to 5 times	Receive either ivabradine or a sugar pill placebo to take by mouth daily for 3 months

Non-Drug Care

In addition to ivabradine or placebo, you will have an equal chance of receiving 3 months of either coordinated non-drug care or usual non-drug care.

What will I do at each clinic visit?

After the screening visit, you will be scheduled to come to the study clinic for the first of several in-person visits. Each visit may last a different amount of time, depending on the study activities you will be asked to complete. Visits that include autonomic nervous system function tests will take longer.

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

- **Baseline Visit (about 5.5 hours):** Complete surveys, lab tests, physical ability tests, and autonomic nervous system function tests (only at specific sites). Enroll in the study and receive your study treatment assignment.
- **1-month Clinic Visit (about 1.5 hours):** Complete surveys and physical ability tests.
- **3-month End of Treatment Visit (about 2 hours):** Complete surveys, lab tests, physical ability tests, and autonomic nervous system function tests (only at specific sites).
- **6-month End of Study Visit (about 2 hours):** Complete surveys and lab tests.

When can I expect the study team to contact me?

- You will receive a follow-up phone call or online survey within one day of the Baseline visit, 1-month clinic visit, and End of Study visit to ask how you are feeling.
- In month 1, a study team member will call you once a week to review how consistently you have taken the study treatment and followed other study requirements including non-drug care activities if you are assigned to the coordinated non-drug care group.
- In months 2 and 3, a study team member will call you once a week to remind you about your coordinated non-drug care activities, if applicable.

About the Active Study Drug: Ivabradine

Researchers are studying ivabradine (pronounced eh-VAH-brah-deen). Ivabradine reduces a person's heart rate without reducing blood pressure or the heart's ability to pump blood. It is given as a pill to take by mouth daily.

Why we are studying it
Ivabradine is approved by the U.S. Food and Drug Administration (FDA) for other uses but not for the treatment of COVID, Long COVID, or POTS. The FDA requires drugs to be studied for each use before it can grant approval.

This study will help us learn if ivabradine can improve symptoms for people who developed POTS after having COVID. Your study team will closely monitor your safety throughout the study.

Notes and Questions for My Study Team

About Your Study Treatment Assignment

You will have an equal chance of being assigned to one of these groups:			
Ivabradine + Coordinated Non-Drug Care	**Placebo + Coordinated Non-Drug Care**	**Ivabradine + Usual Non-Drug Care**	**Placebo + Usual Non-Drug Care**

- **Ivabradine** is the active study drug.
- The **placebo** looks like the active study drug but has no active ingredients and should have no effect.
- **Coordinated non-drug care** includes specific recommendations for diet and lifestyle changes such as wearing a compression belt around the stomach, eating a high-salt diet, increasing the amount of fluids you drink, and physical activities.
- **Usual non-drug care** includes general recommendations for diet and lifestyle changes.

All participants are valuable contributors to this study. Without the placebo and usual non-drug care to use as points of comparison, researchers would not be able to learn how the active study treatments affect participants' health and Long COVID symptoms.

You will know if you have been assigned to the coordinated non-drug care or usual non-drug care group. However, you, your study doctor, and the study team will not know whether you are receiving the active study drug or placebo, but they can quickly find out if there is ever a need to know for your safety or well-being.

Important Reminders for Taking Ivabradine or Placebo

Taking the study drug

- Take the pill by mouth daily for 3 months.
- Swallow the pill whole. Do not break or crush the pillows before swallowing.
- Your dose of the study drug may be changed if needed based on your heart rate at the 1-month clinic visit.
- Store the pills at room temperature (67°F to 77°F).

Missed doses

- If you miss a dose of the study drug within 8 hours of the time it is usually taken, take it as soon as possible and then continue your normal dosing schedule.
- If you miss a dose of the study drug by more than 8 hours, do not take the missed dose. Instead, take the next dose at the regularly scheduled time.
- Do not double the dose to make up for a missed dose.

More About the Non-Drug Care Groups

In addition to the study drug or placebo, participants will have an equal chance of being assigned to 1 of these non-drug care groups:

<table>
<tr><th>Coordinated Non-Drug Care</th><th>Usual Non-Drug Care</th></tr>
<tr><td>If you are enrolled in this group, you will receive:
• A blood pressure and heart rate machine (including 4 AA batteries)
• Salt measurement spoons (including one teaspoon, one 3/4 teaspoon, and one leveler)
• A 1-liter (32-ounce) water bottle
• A compression belt to wear around your stomach while doing upright activities
• A yoga mat
• Latex stretch bands (including 5 different strengths: Extra Light, Light, Medium, Heavy, and Extra Heavy)
• A fitness tracker (Fitbit)
• A weekly activity log</td><td rowspan="3">If you are enrolled in this group, you will receive the usual healthcare guidelines you may receive as part of your normal or routine healthcare, such as general recommendations for diet and lifestyle changes.</td></tr>
<tr><td>You will be asked to complete additional study activities from home for the first 12 weeks (3 months) of the study. You will also be asked to record certain activities in a weekly log. Activities include checking your blood pressure and heart rate, eating salt, drinking water, wearing a compression belt, and completing physical activities.</td></tr>
<tr><td>A care coordinator will contact you once a week for 3 months to provide support on these activities.</td></tr>
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More About the Fitness Tracker

During the study intervention period, you will be asked to wear a fitness tracker on your wrist, similar to a watch, to record various health data, which are automatically captured by the fitness tracker.

- You are encouraged to wear it during the entire study. However, you are required to wear it for 7 days after your Baseline visit and 7 days before your End of Treatment Visit.

If you do not have a mobile device or data plan that will work with the fitness tracker, then one may be provided. If you are provided a mobile device as part of this study, you may keep it after the study ends.

About the RECOVER Research Biorepository

A biorepository is designed to collect and store biospecimens for future research. In this study, we have biorepositories for biospecimens that may include samples of blood, stool (poop), and skin. 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 our biorepositories. **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 a "biomarker." 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 our biorepositories may:

- Increase the possibility of developing new possible treatments related to Long COVID
- Improve our understanding of how possible treatments 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 treatment.

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. You will not be notified if or when your samples are used for future research.

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 each specified study visit. See "blood sample" on the participant schedule for more information about when blood draws will occur.

Stool Samples

How will I provide stool samples?
After the Baseline and End of Study Treatment 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 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 (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.

RECOVER-AUTONOMIC Ivabradine or Placebo Participant Schedule

STUDY ACTIVITIES: About 6 months

Pre-Study Period (3 weeks)

Baseline Visit (about 5.5 hours) Date:	Information	Assessments	Receive
	• Review current medicines • Review study requirements • After this visit, complete a survey about how you are feeling	• Surveys • Blood sample • Nasal swab sample • Physical ability tests • Safety check • Pregnancy test, if needed • Autonomic nervous system function tests (only at specific sites)	• Study drug (ivabradine or placebo) • At-home stool (poop) sample kit • Fitness tracker **Coordinated non-drug care group** • Blood pressure and heart rate machine • Salt measurement spoons • Water bottle • Compression belt • Yoga mat • Latex stretch bands • Physical activity training guidelines • Weekly activity log **Usual non-drug care group** • Magnet with guidance on lifestyle and diet changes

Study Treatment Period (3 months)

Begin the Study Drug	• Take the study drug by mouth every day for 3 months. • Your dose of the study drug may be changed if needed based on your heart rate at the 1-month clinic visit.
Begin Coordinated Non-Drug Care, If Assigned	• If you are in this group, you will be asked to complete a non-drug care log to record your activities at the end of each week. • Activities include checking your blood pressure and heart rate, eating salt, drinking water, wearing a compression belt, and completing physical activities. • A care coordinator will contact you once a week for 3 months to provide support on these activities.

Study Treatment Period (3 months), continued		
1-month Clinic Visit (about 1.5 hours) **Date:**	**Information** • Review medicines • Review how consistently you have taken the study drug • After this visit, complete a survey about how you are feeling	**Assessments** • Surveys • Physical ability tests • Safety check
3-month End of Treatment Visit (about 2 hours) **Date:**	**Information** • Review medicines • Review how consistently you have taken the study drug • After this visit, complete a survey about how you are feeling	**Assessments** • Surveys • Physical ability tests • Blood sample • At-home stool (poop) sample kit • Safety check • Autonomic nervous system function tests (only at specific sites)
Follow-Up: End of Study (3 months later)		
6-month End of Study Visit (about 2 hours) **Date:**	**Information** • Review medicines • After this visit, complete a survey about how you are feeling	**Assessments** • Surveys • Physical ability tests • Blood sample • 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 prescribed or over-the-counter medicines or have a change in any of your current medicines
- Change your phone number, email, or home address
- Have questions about the study or the study treatments
- Become pregnant or think you might be pregnant

Site Contact Information

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

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