Study Title: Repurposing a histamine antagonist to benefit patients with pulmonary hypertension (REHAB-PH)

National Clinical Trial (NCT) Identified Number: NCT03554291

PI Name: Peter Leary, MD PhD

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UNIVERSITY OF WASHINGTON
CONSENT FORM

Repurposing a Histamine Antagonist to Benefit Patients with Pulmonary Hypertension (REHAB-PH)

Researchers:

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24-hour emergency telephone number: (206) 598-6190

The above number will reach University of Washington Medical Center; ask the operator to page Dr. Peter Leary.

Researchers' statement

We are asking you to be in a research study. The purpose of this consent form is to give you the information you will need to help you decide whether to be in the study or not. Please read the form carefully. You may ask questions about the purpose of the research, what we would ask you to do, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions, you can decide if you want to be in the study or not. This process is called "informed consent." We will give you a copy of this form for your records.

PURPOSE OF THE STUDY

We would like to better understand right heart failure in patients with pulmonary arterial hypertension (PAH). This clinical trial is testing to see if an over-the-counter drug, famotidine, will improve ability to exercise and right heart function in participants with PAH. Famotidine is an FDA-approved drug used to treat symptoms of heartburn. In this study we are testing famotidine for an unapproved use in participants with right heart failure. We are enrolling up to 80 participants at the University of Washington. We are asking you to be in this trial because you are currently being treated for PAH at the University of Washington.

STUDY PROCEDURES

If you agree to be in this study, you will be randomized into one of two groups. Randomization means that you are placed into a group by chance and will have an equal chance of being placed in either the group receiving famotidine or the group receiving placebo. A placebo is a "sugar tablet" made to look like the investigational drug. This study is considered a 'double blind' study. This means that neither you nor the study doctor will be aware of which group you are assigned to.

This study will last 24 weeks from the time of enrollment and consists of two or three in-person visits and one phone call. A phone call will be made at Week 4 and in-person visits will be at Baseline and Week 24. The Week 12 visit may be done in person of via phone. Each in person visit will be at the University of Washington Medical Center Pulmonary Vascular Disease Clinic and will add about an additional 20-30 minutes to your normal clinic visit.

Baseline Visit

At the baseline visit, you will be consented and eligibility will be assessed. You will undergo a standardized clinical assessment, which includes vital signs, weight, a physical examination, a review of your medical history, demographics, medications, and an assessment of your symptoms. Blood will be collected for routine tests. If you are of child-bearing potential, we will also do a pregnancy test by blood serum or urineIf positive, you will be ineligible for the study. You must also agree to the use of effective contraception.

You will be asked to complete a 6-minute walk distance (6MWD). You will be asked to walk for 6 minutes while someone times you and watches to evaluate the distance you can travel within the 6 minutes. You can let them know you want to stop at any time. You will also be asked to complete a short questionnaire designed to determine how pulmonary hypertension affects your life. In addition, an echocardiogram will be scheduled and will take about 60 minutes. An echocardiogram is a sonogram of the heart.

Sub-studies will be described in a later section and include right heart catheterizations and/or cardiopulmonary exercise tests (CPET) at Baseline and Week 24. Each test will take about 2 hours. Participants may elect to do either, both, or neither sub-study. For individuals who want to participate in both sub-studies, these can be performed on the same or different days as long as they are within 14 days of the baseline visit and within 7 days of the Week 24 visit. If you choose to do both sub-studies on the same day, the CPET will be performed prior to the right heart catheterization.

For most participants in the main study, all study assessments will occur during one study visit; however, sub-study participants and occasional main study participants may have study assessments on two or more different days. If this occurs then randomization will occur following the last baseline study assessment. You may go through baseline procedures and not qualify for the study.

Study drug will be dispensed on the day of the last study assessment and will be started the day following the last baseline assessment. All baseline assessments must be completed over the 14 days before study drug is started. A study physician will also provide Tums and Omeprazole as needed for short and long term heartburn control. We hope that you will use only these medications for heartburn, but will also give you a list of medications to avoid if buying over-the-counter heartburn medication since some of these may be the study drug (famotidine) or similar drugs. Use of these medications could invalidate the trial.

Week 4 Phone Call

A phone call will be made on day 28 ± 7 to assess study drug compliance and adverse events.

Week 12 Visit

At Week 12, day 84 ± 7, you will undergo a standard clinical assessment, which includes vital signs, weight, a physical examination, a review of your medications, and an assessment of your symptoms. You will be asked to complete a 6MWD and a questionnaire designed to determine how pulmonary hypertension affects your life. Study drug will be dispensed at this visit and you will be instructed to take one tablet daily (20 mg of famotidine or placebo). Due to the COVID-19 pandemic, this visit may be done in person or as a phone call based on the prevalence of COVID-19 in the community or preference. We encourage you to come to this visit in person, if possible. If done via phone this visit will include a symptom assessment, a review of your medications and a questionnaire. The Investigational Drug Service at UWMC will ship the next supply of study medication to your home via FedEx overnight prior to this visit.

Week 24 Visit

Similar to the Baseline visit, Week 24, day 168 ± 7, you will undergo a standard clinical assessment, which includes vital signs, weight, a physical examination, a review of your medications, and an assessment of your symptoms. You will be asked to complete a 6MWD, a questionnaire, and an echocardiogram. Blood will be collected for routine tests and a pregnancy test either by blood serum or urine if you are of child bearing potential. Individuals who participate in the exercise sub-study, right heart catheterization sub-study, or both sub-studies will repeat the exercise and/or heart catheterization within 7 days of the final visit. The Week 24 visit must be done while taking study drug and thus, study drug will be returned after all Week 24 assessments, including the sub-studies, have been completed.

OPTIONAL OPT-OUT STUDY PROCEDURE

Additional blood, up to 32 ml (2.2 tablespoons), will be collected and stored at your Baseline and Week 24 visit. This blood is in addition to the non-optional blood draw described above and does not involve a separate needle “poke”. This additional blood will be stored and may be used over time to help understand potential markers important to patients with pulmonary hypertension and/or right heart failure. Such markers may include tests for proteins, RNA and other components of blood. RNA is a genetic material that has a major role in making proteins. This evaluation is not required to take part in the study. You retain the right to contact the study team at any time in the future and withdraw your consent.

OPTIONAL OPT-IN RIGHT HEART CATHETERIZATION EVALUATION

This evaluation is not required in order to take part in the study. If you choose to take part in this evaluation, this test will be performed at the Baseline Visit and at the last visit, Week 24. The right heart catheterization will be scheduled within 14 days of your Baseline Visit AND within 7 days of your Week 24 Visit. The baseline visit must be done while not taking study drug and the week 24 visit must be done while taking study drug. This is a procedure which is performed frequently for patients with PAH and everyone considered for the study will have had a least one right heart catheterization to diagnose their disease. The purpose of this optional evaluation is to track changes in the measurements of your heart and lungs that might be related to study

treatment with famotidine. You should allow 3-4 hours to complete the right heart catheterization. On the day of your right heart catheterization you will check into the cardiac catheterization laboratory at the University of Washington Medical Center. A nurse will check you vital signs and basic bloodwork to make sure that the procedure is safe to perform. Once this is done, you will go into the cardiac catheterization laboratory where Dr. Leary will numb the area for the procedure with lidocaine. This will typically be the right side of your neck. After numbing the area, Dr. Leary will place a catheter into a vein, the right atria, right ventricle, and pulmonary artery. He will measure pressures at each position and check to see how much blood your heart is pumping. The process of inserting the catheter and taking measurements normally takes approximately 20-30 minutes. After these measurements, the catheter will removed, a nurse will hold pressure on the area to ensure that there is no bleeding, and then you will be free to go.

OPTIONAL OPT-IN CARDIOPULMONARY EXERCISE TEST EVALUATION

This evaluation is not required in order to take part in the study. If you choose to take part in this evaluation, this test will be performed at the Baseline Visit and at the last visit, Week 24. The cardiopulmonary exercise test (CPET) will be scheduled within 14 days of your Baseline Visit and within 7 days of the Week 24 Visit. The baseline visit must be done while not taking study drug and the week 24 visit must be done while taking study drug. If you choose to take part in the CPET, this will be done via bicycle ergometry and will be performed in the Exercise Testing Laboratory of the UW Lung Function Testing Center. This is a routine clinical test used by pulmonologists and cardiologists, but unlike the right heart catheterization, is not routinely done for all individuals with PAH. In this test we measure how well your body tolerates physical activity. Due to the COVID-19 Pandemic, the Lung Function Testing department at UWMC is requiring novel coronavirus testing prior to any procedures done in the lab. As long as this requirement is in place, you will be given a phone number to call to arrange testing at a drive through testing site within 72 hours of your appointment. At the drive through site, you will stay in your car and a nurse will use a nasal swab (like a long Q-tip) inserted into your nose and back of throat to collect cells which will be sent to the lab. You will be notified in the event of a positive test result.

On the day of the test, you will check into the Lung Function Testing Center at the University of Washington Medical Center. You should wear clothing suitable for exercise. A respiratory therapist will check your vital signs and conduct breathing tests. After this they will hook up an EKG, monitor your oxygen via a probe on your finger, and place a neoprene mask over your nose and mouth. These will measure a number of important exercise characteristics. You will then ride a stationary bicycle in the exercise lab. The test is variable in length and designed to push you to exercise as hard as you can tolerate in a highly supervised setting. Most participants exercise for 5-15 minutes with increasing resistance on the stationary bicycle. This is followed by a “cool-down” period on the bicycle. When you are done, a respiratory therapist will continue to monitor you for 5-10 minutes at rest. After this time, you will be free to go.

Some information may be abstracted from your medical record if you have already had tests done for clinical care (such as six-minute walk distance, safety labs, and one echocardiogram).

A table summarizing most of the study procedures and schedule can be found below.

Study drug will be dispensed on the day of the last study assessment and will be started the day following the last baseline assessment. Study drug compliance will be assessed at the Week 4 phone call, Week 12 visit, and the Week 24 visit.

	Baseline Visit	Week 4 Phone Call	Week 12 Visit	Week 24 Visit
Visit #	1	Phone Call	2	3
Informed Consent	X			
History and Physical Exam	X		X	X
Blood draw	X			X
Pregnancy test if premenopausal	X			X
6 minute-walk distance	X		X	X
Echocardiogram	X			X
Questionnaire	X		X	X
OPTIONAL Testing				
Right heart catheterization	X			X
Cardiopulmonary Exercise Test	X			X
Covid testing for exercise testing (as required per lab requirement)	X			X

Although the baseline visit can be completed in a single visit in most cases, all testing in the baseline visit must be completed within 14 days. Similarly, all testing in the week 12 and week 24 visits must be completed within 7 days of the assigned date (if Week 12 is remote, there will be no 6MWD or physical exam)

RISKS, STRESS, OR DISCOMFORT

While we use every effort to protect your personal information, absolute confidentiality cannot be guaranteed and is always a potential risk of participation in research.

You may be uncomfortable with some of the questions and/or uncertainty of whether you are taking the study drug or placebo. Please remember that if you decide to participate, you can skip any question for any reason.

If you were taking a medication like famotidine for heartburn symptoms and are assigned to placebo for this study, you may have worsening of your heartburn symptoms. The investigators can provide medicines to treat your symptoms such as calcium carbonate and omeprazole.

Famotidine is very well tolerated and available over-the-counter where it is commonly marketed as Pepcid. Headaches and gastrointestinal upset have been reported and very rare instances of allergic reactions to the medication (e.g. hives or difficulty breathing).

The blood draws may cause some temporary discomfort and may include pain at the needle insertion site, slight bruising, or development of a small hematoma. There is a small risk of

infection at the needle insertion site. Some people become anxious with blood draws and are prone to fainting.

There are few risks associated with a six-minute walk test since you decide how fast to walk depending on your ability. Changes in blood pressure, heart rate, and fainting can happen.

During the echocardiography, discomfort during the acquisition of images is possible.

Right heart catheterization risks include temporary discomfort and may include pain at the needle insertion site, chest pain, nausea, vomiting, dizziness, fainting, temporary high or low blood pressure, slight bruising, or development of a small hematoma/bleeding. The topical lidocaine injection can cause redness, irritation or allergic reactions in rare instances (e.g. hives or difficulty breathing). Fewer than one in five hundred procedures may be complicated by infection requiring antibiotics, surgery to correct if there is damage to the blood vessel or heart valves, surgery to remove air if there is lung collapse, or blood thinners if a blood clot develops in the vein. It is also possible to develop an abnormal or potentially dangerous heart rhythm requiring drugs or electrical shocks during the procedure. Death has been reported in very rare cases.

Dr. Leary performs 6-12 right heart catheterizations every week and has done more than 2,000 right heart catheterizations over the course of his career. He has had one complication while supervising a trainee requiring overnight hospitalization (lung collapse) to correct and will do all of the heart catheterizations for this study personally without trainees. If Dr. Leary is physically unable to do the right heart catheterization within the study mandated time window, Dr. Steinberg, an interventional cardiology attending, will do the procedure.

Cardiopulmonary exercise testing (CPET) risks include changes in blood pressure and heart rate, discomfort, increased risk for fainting and the potential for you to develop an abnormal heart rhythm during the test. In rare circumstances, there can be serious complications such musculoskeletal injury, heart attack, or stroke. Death has been reported in very rare cases.

The Covid testing may cause some discomfort from having a swab inserted in your nose and throat. It may cause coughing and a gagging feeling or cause a burning sensation and eye watering. Occasionally people feel some irritation in their nose or throat for several hours after the test.

Pulmonary arterial hypertension is a serious disease. Some problems are more common for patients with this disease regardless of whether or not they participate in a study. These problems include dizziness, fainting, leg swelling, abdominal swelling, chest pain, shortness of breath, low oxygen, coughing up blood, nausea, vomiting, diarrhea, jaw pain, flushing, joint pain, muscle pain, infection, abnormal heart rhythm, heart failure, pericardial effusion (fluid around the heart), abnormalities in blood counts, abnormalities in kidney function and electrolytes, cirrhosis (damage to the liver), blood clots, stroke, cardiac arrest, and death.

For women of childbearing potential, pregnancy and the post-partum period is a highly dangerous and volatile time for women with pulmonary arterial hypertension and as a result, if you are currently pregnant, lactating, or have evidence of dynamic disease with pulmonary vasodilator adjustment within 30 days of randomization, you will not be able to participate in the

study. If you are able to become pregnant, you will be given a serum pregnancy test before entry into the study. You are asked to use a dual-method of contraception while participating in the study. You should not become pregnant while in the study. If you do become pregnant, you must inform the study coordinator.

There may be risks related to the study procedures that are not yet known to the researchers. This includes unanticipated side effects from the use of the drug. As this is an investigational drug, you will be updated with any learned information during the study that may affect your willingness to participate.

There is a possibility that you may be withdrawn from the study. This may occur if Dr. Leary and/or your other pulmonary hypertension physician(s) feel that your continuation in the study would be detrimental to your well-being, a serious adverse event occurs due to the trial medication, any relevant deterioration in your health occurs, the protocol is violated, or you are unable to stay on the study drug or off other H_2 blockers. If you are female and of childbearing potential, you will be withdrawn if you become pregnant.

ALTERNATIVES TO TAKING PART IN THIS STUDY

You are free not to participate in this clinical study and will continue to receive the same high quality care that you have always received with no impact on your current treatment. Please take your time to make your decision about taking part in this study. You may discuss your decision with your friends and family. You can also discuss it with your healthcare team. If you have any questions or concerns, you can ask the study doctor for more explanation.

BENEFITS OF THE STUDY

We hope that the results of this study will help patients with pulmonary hypertension in the future. It is possible that if you receive famotidine, you will experience an improved functional capacity and improved metrics of right heart failure relative to those who receive placebo. Some participants will not receive any direct benefit, though some people might find satisfaction in contributing to scientific knowledge about their disease.

COSTS

If you choose to participate in the study, you do not have to pay for study drug and Omeprazole and Tums, study visits, and tests that have to be done for the study. You or your insurance company will have to pay for routine care, such as clinic visits and some echocardiograms, walk tests, and blood work that you would receive whether or not you are in the study. Researchers will access your medical record to obtain these results. You may talk to the study staff and your insurance company about what is covered.

SOURCE OF FUNDING

The study team and the University of Washington are receiving financial support for this study from the National Institute of Health/National Heart, Lung, and Blood Institute.

CONFIDENTIALITY OF RESEARCH INFORMATION

Data collected about you for this study will be kept in the research record. Identifiable information will be coded and linked to study information. This information and all study data will be kept on a password secured computer database.

Any publications regarding the results of this study will not include any information that would identify you. De-identified data may be used for future studies. Participating in this study is completely voluntary. Even if you decide to participate now, you may change your mind and stop at any time.

Government or university staff sometimes review studies such as this one to make sure they are being done safely and legally. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm.

The U.S. Food and Drug Administration (FDA) reserves the right to review study data that may contain identifying information.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time (Clinical trials identifier: *NCT03554291)*

Your participation in this study will be noted in your UW medical record.

We have a Certificate of Confidentiality from the federal National Institutes of Health. This helps us protect your privacy. The Certificate means that we do not have to give out identifying information about you even if we are asked to by a court of law. We will use the Certificate to resist any demands for identifying information.

We can't use the Certificate to withhold your research information from you if you give your written consent to give it to an insurer, employer, or other person. Also, you or a member of your family can share information about yourself or your part in this research if you wish.

There are some limits to this protection. We will voluntarily provide the information to:

- a member of the federal government who needs it in order to audit or evaluate the research;
- individuals at the University of Washington, the funding agency, and other groups involved in the research, if they need the information to make sure the research is being done correctly;
- the federal Food and Drug Administration (FDA), if required by the FDA;
- authorities, if we learn of child abuse, elder abuse, or the intent to harm yourself or others.

USE OF INFORMATION AND SPECIMENS

Genetic Testing

If you participate in the optional *opt-out* study of RNA, we will also perform a genetic analysis of your blood sample focused on a specific kind of genetic code known as RNA. Usually researchers study just a few areas of your genetic code that are linked to a disease or condition, but for this study, all or most of your genes will be analyzed and used by researchers to study links to many diseases and conditions.

Using Your Data in Future Research

The information and/or specimens that we obtain from you for this study might be used for future studies. We may remove anything that might identify you from the information and specimens. If we do so, that information and specimens may then be used for future research studies or given to another investigator without getting additional permission from you. It is also possible that in the future we may want to use or share study information that might identify you. If we do, a review board will decide whether or not we need to get additional permission from you.

GENOMIC DATA SHARING

The National Institutes of Health (NIH) has developed data (information) banks that collect study data. The NIH will store your de-identified information in these data banks for other researchers to use in future studies on any topic. The researchers could be from government, academic, or commercial institutions.

If you participate in the optional *opt-out* genetic study of RNA, the information from this study may be stored in a public unrestricted data bank that anyone can use. This public information will not include your name or other information that could identify you. It is possible that your genomic information could be used to identify you when combined with information from other public sources, but we believe this is unlikely to happen. You will not receive any results from allowing your data to be placed in the NIH data banks. You will not be able to withdraw your information after it has been submitted to the NIH data banks.

If you participate in the optional *opt-out* genetic study of RNA, there is a risk that others will be able to trace this information back to you or close biological relatives. The current risk of this happening is very small, but may grow in the future as new technologies are developed. If this should happen, someone might use this information to learn something about your health or genetic heritage. If linked to a medical condition and inappropriately shared with someone, it could affect your ability to get or keep some kinds of insurance. There is a possibility that this information could affect family members because certain conditions and traits run in families and are inherited through genes. This could hurt family or other relationships. There is a risk that your information could become known to the public, employers, or law enforcement agencies. The information may be used to enforce negative stereotypes.

There may also be other risks that are not yet known.

OTHER INFORMATION

You may refuse to participate and you are free to withdraw from this study at any time. If you choose to do so then you will still continue to receive the same high quality care that you received before participating and during the study.

You will be compensated $100 for each in-person visit to the University of Washington, which will cover parking, travel costs, and other incidentals. You will receive $25 for the Week 12 visit if done remotely.

Blood collected as part of this study will be stored in a locked research laboratory in the Division of Pulmonary, Critical Care, and Sleep Medicine. Blood will be identified only by your identification code and the link between this code and your personally identifying information will be maintained in a password secured computer database.

Results from standard clinical tests will be returned to you and the results may affect the need to add additional PAH therapy, adjust diuretics, and consider advanced treatments like lung transplant.

RESEARCH-RELATED INJURY

If you think you have been harmed from being in this research or have a medical problem or illness related to this research, contact the study staff listed at the beginning of the consent form right away. The study staff will treat you or refer you for treatment.

It is important that you promptly tell the researchers if you believe that you have been injured because of taking part in this study. You can tell the researcher in person or call him/her at the number(s) listed at the top of this form. This number is monitored 24 hours a day.

If you are injured as a result of being in this study, necessary medical treatment will be offered at a UW Medicine facility.

The costs of the treatment may be billed to you or your health insurance just like other medical costs, or it may be covered by the UW's discretionary Human Subjects Assistance Program (HSAP), depending on a number of factors. The researcher may request HSAP coverage by following established procedures. If you wish to request HSAP coverage yourself, contact the researcher or the UW Human Subjects Division at hsdinfo@uw.edu or 206-543-0098. You may also call collect to the UW Human Subjects Division at 206-221-5940 if you do not otherwise have access to a telephone. Ask the researcher if you would like information about the limits and conditions of the HSAP. The UW does not normally provide any other form of compensation for injury. However, the law may allow you to seek payment for injury-related expenses if they are caused by malpractice or the fault of the researchers. You do not waive any right to seek payment by signing this consent form. We will bill your health insurance for treating problems that result from your pulmonary arterial hypertension or from standard clinical care. If you have no health insurance or your insurance refuses to pay, we will bill you.

If you have questions about the research, please contact one of the researchers listed on this form. If you have questions about your rights as a research subject, please contact the University of Washington Human Subjects Division at (206) 543-0098.

❑ Please do not include me in the RNA isolation and stored blood as described in the optional section of this consent form. _____ Initials

I would like to participate in the right heart catherization sub-study. ❑ Yes ❑No _____ Initials

I would like to participate in the cardiopulmonary exercise test sub-study. ❑ Yes ❑No _____ Initials

You may contact me in the future about other studies. ❑ Yes ❑No _____Initials

Printed name of study staff obtaining consent* Signature* Date*

Subject's statement

This study has been explained to me. I volunteer to take part in this research. I have had a chance to ask questions. If I have questions later about the research, or if I have been harmed by participating in this study, I can contact one of the researchers listed on the first page of this consent form. If I have questions about my rights as a research subject, I can call the Human Subjects Division at (206) 543-0098 or call collect at (206) 221-5940. I give permission to the researchers to use my medical records as described in this consent form. I will receive a copy of this consent form.

Printed name of subject Signature of subject Date

E-mail address if you consent to the use of e-mail in order to contact you

Copies to: Subject
Investigator's file