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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Clinical Trial Protocol: REHAB-PH

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(REHAB-PH)

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Principal Investigator: Peter Leary, M.D., Ph.D.

Funded by: National Heart, Lung, and Blood Institute

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

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

Study Description: Pulmonary arterial hypertension (PAH) is one of many conditions that put stress and strain on the right side of the heart. This stress and strain can cause right heart failure. Although there are medications to treat PAH, there are currently no medications that act directly on the heart to improve right heart function. This is different than left heart failure where one of the cornerstones of treatment is medication targeted at the heart to improve left heart function.

Famotidine is a well-tolerated, over-the-counter, and inexpensive medication. Preliminary results suggest that famotidine may help the right heart to adapt and strengthen when stressed instead of fail; however, these results are suggestive and not definitive. A randomized controlled trial is required to evaluate the possibility that famotidine can impact right heart function.

Objectives:

Primary Objective:

To determine whether famotidine increases six-minute walk distance at 24 weeks in men and women with pulmonary arterial hypertension.

Secondary Objectives:

- To determine whether famotidine reduces BNP at 24 weeks
- To determine whether famotidine improves New York Heart Association (NYHA) functional class at 24 weeks
- To determine whether famotidine improves right ventricular morphology at 24 weeks including improved right ventricular diameter and TAPSE
- To determine whether famotidine improves health related quality of life as estimated by the emPHasis-10 score
- To determine whether famotidine decreases the need to escalate PAH focused care (increased diuretics, escalating doses of pulmonary vasodilators, and/or adding an additional pulmonary vasodilator)
- To explore changes in invasive hemodynamics with famotidine
- To explore changes in gas exchange, maximal oxygen uptake, metabolism, and myocardial reserve with famotidine

Sub-study Objectives:

Exercise sub-study:

- To determine whether famotidine increases maximal oxygen uptake in individuals with pulmonary arterial hypertension at 24 weeks
- To explore changes in other metrics of the exercise response (oxygen uptake, Ve/VCO2 ratio, total achieved wattage) with famotidine relative to placebo over 24 weeks.
- In a "right heart targeted therapy" trial, to explore the relationship between markers of the exercise response and other standard markers of treatment response including BNP, New York Heart Association functional class, quality of life, and need to escalate PAH-specific therapy.

Right heart catheterization sub-study

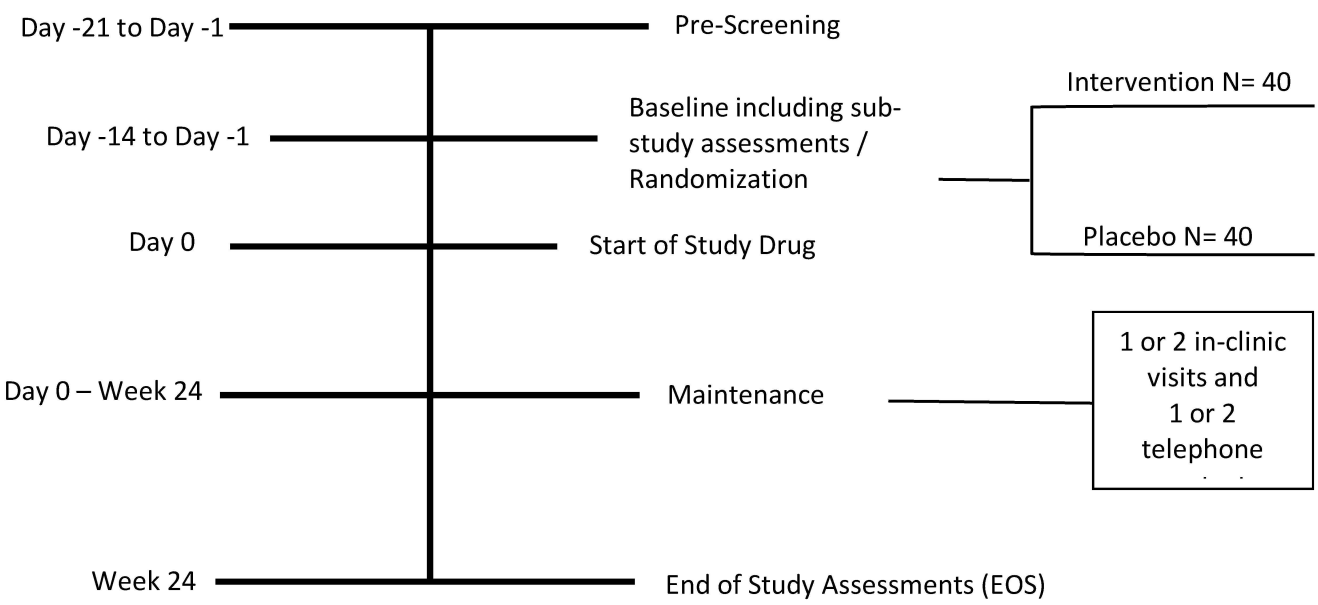
- To determine whether famotidine increases stroke volume index at 24 weeks
- To explore whether famotidine is associated with differences in wedge pressure, right atrial pressure, and/or pulmonary vascular resistance at 24 weeks
- In a "right heart targeted therapy" trial, to explore the relationship between markers of the exercise response and other standard markers of treatment response including BNP, New York Heart Association functional class, quality of life, and need to escalate PAH-specific therapy.

Endpoints:

Primary endpoint: The difference between treatment groups in 6-minute walk distance (6MWD) at 24 weeks.

	Secondary endpoint: The difference between treatment groups in BNP, NYHA functional class, TAPSE, right ventricular basal diameter, emPHasis-10 score, and number of participants with an escalation of routine clinical treatments for PAH for each visit.
Study Population:	Approximately 80 participants, male or female, age 18 to 80 with WHO Group 1 Pulmonary Arterial Hypertension and NYHA Functional Class II, III, or IV at screening.
Phase:	II
Description of Sites/Facilities Enrolling Participants:	All potential subjects for the REHAB-PH Trial will be recruited from the University of Washington Pulmonary Vascular Disease Program.
Description of Study Intervention:	Famotidine, 20 mg daily, per oral
Study Duration:	60 months
Participant Duration:	Participants will be evaluated and participate over 24 ± 1 weeks.

1.2 SCHEMA



All patients in the pulmonary vascular disease clinic are pre-screened using the electronic medical record.

Those interested in participation and eligible will be consented at their baseline visit. 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. Individuals who appear to violate inclusion or exclusion criteria as a result of baseline assessments before randomization will be considered screen failures and not randomized.

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. Study drug start date will be considered Day 0.

1.3 SCHEDULE OF ACTIVITIES (SOA)

	Baseline	**Randomization**		**Phone Visit Week 4**	**Week 12**	**Week 24**
Visit #	1		Non-visit	PH	2	3
Day #	-14 to -1	-1	0	28 ± 7	84 ± 7	168 ± 7
Inclusion/Exclusion Criteria	X					
Informed Consent	X					
History and physical exam						
Demographics	X					
Medical history	X					
Symptom assessment	X				X	X
Concomitant medications	X				X	X
Vital Signs & Weight	X				**X	X
Physical Examination	X				**X	X
Safety laboratories						
Laboratory Draw	X					X
Comprehensive metabolic panel	X					X
Complete blood count	X					X
Mass-Spectrometry for H_2 antagonists	X					X
Pregnancy test if premenopausal	X					X
Endpoint assessment						
6 minute-walk distance (primary)	X				** X	X
echocardiogram	X					X
emPHasis-10 score	X				X	X
BNP	X					X
NYHA functional class	X				X	X
Study Procedures						
Dispense study drug		X			X	
Start study drug			X			
Study drug adherence				X	X	X
Study drug compliance				X	X	X
Adverse events	X			X	X	X
Study Termination						X
Sub-study components						
Right heart catheterization (n=20)	X					X
Cardiopulmonary Exercise Test (n=10)	X					X
Covid testing for exercise test (as required per lab requirement)	X					X
Miscellaneous						

Data Safety Monitoring Board	Semi-annually

As per clinical practice guidelines, patients will be seen every three to six months with blood work and six-minute walk testing. These elements (visit, laboratory draw, comprehensive metabolic panel, complete blood count, BNP, pregnancy test, 6 minute-walk distance, and NYHA functional class) will be collected as part of routine medical care and abstracted from the medical record as research endpoints. The pregnancy test can be performed as either a blood or urine test. A blood-based pregnancy test is preferred; however, if a urine test is used then it must be performed by study personnel and documented in the medical record. Echocardiograms are often part of routine medical care and will be abstracted from the medical record as research endpoints; however, the frequency may be influenced by the study. To avoid any concern about overlap, any echocardiogram occurring more frequently than annually will be considered research. It is anticipated that 1 of the 2 echocardiograms will fit this research definition. Other research elements include mass spectrometry for H_2 antagonists, the emPHasis-10 score, study procedures, and sub-study components.

** These procedures will not be performed if the visit is done remotely.

2 INTRODUCTION

2.1 STUDY RATIONALE

Although there has been substantial progress in the development of medications to lower pulmonary vascular resistance in pulmonary arterial hypertension, there are currently no therapies that have been shown to have benefit for right heart failure in the absence of changes in right ventricular afterload.

We are pursuing a novel approach that targets histamine H2 receptors in patients with pulmonary arterial hypertension. Previous animal studies suggest that myocardial H2 receptors contribute to myocardial fibrosis and are important mediators of heart failure. Our work has shown a lower incidence of heart failure in community dwelling adults who use H2 receptor antagonists and a lower all-cause mortality in veterans with pulmonary hypertension who use H2 receptor antagonists. A previous randomized controlled trial showed that famotidine improved b-natriuretic peptide, left ventricular morphology, and New York Heart Association Functional Class in participants with Heart Failure and Reduced Ejection Fraction (left heart failure). H2 receptor antagonism is an appealing therapeutic target that is well aligned with current NIH priorities of repurposing existing, inexpensive, and well-tolerated medications for novel use in other disease states.

We will study intermediate range clinical efficacy of famotidine in participants with pulmonary hypertension. We will also assess the safety of famotidine in participants with pulmonary hypertension.

There are two sub-studies proposed for the REHAB-PH trial. One sub-study involves cardiopulmonary exercise testing and the other sub-study involves invasive hemodynamic evaluation using right heart catheterization. Understanding the relationship between therapy, exercise response, and invasive hemodynamic assessment is important for all pulmonary arterial hypertension (PAH) therapies and such studies are very common in trials of PAH-specific therapy. To date, nearly all therapeutic trials for participants with PAH have focused on medications intended to lower pulmonary vascular resistance and right heart afterload. Few studies have evaluated therapies intended to improve right heart fitness in the absence of changes in right heart afterload (“right heart targeted therapy”). Targeting myocardial

histamine H2 receptors is one such therapy that is hypothesized to impact right heart fitness without changing right heart afterload. While the two proposed sub-studies are powered to detect plausible, but large differences in exercise response or invasive hemodynamic markers, these studies are not powered to detect small to moderate differences. The co-primary intent of these sub-studies is to begin to understand appropriate end-points in trials of right heart targeted therapy. This more exploratory motivation is intended to complement but not supplant primary and secondary outcome measures including six-minute walk distance, BNP, and right ventricular structure and function by echocardiography in the current trial. Lessons learned from resting, exercise, and invasive measures will be used to inform subsequent trials of right heart targeted therapy using famotidine and/or other compounds. We will study exercise response and invasive hemodynamic differences in participants with pulmonary hypertension with and without exposure to famotidine.

2.2 BACKGROUND

H2 receptor antagonists were used successfully as a treatment for left heart failure and we showed a lower incidence of heart failure and differences in cardiac morphology with H2 receptor antagonist use in a large observational cohort. We have also shown H2 receptor antagonist use is associated with improved mortality in a cohort of veterans with pulmonary hypertension. This raises the strong possibility that H2 receptor antagonism is important in heart failure and likely alters the natural history of right heart failure.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 POTENTIAL RISKS

Protection of participant identity is important and will be safeguarded by the use of study identifiers whenever possible, a secure comprehensive data management system, and safeguards for electronic data including password protection and encryption. In addition, all study staff will be trained in the importance and proper safeguards for participant's privacy and confidentiality. All study personnel will be required to sign a confidentiality agreement as per our institutional review board requirements.

All other study procedures including venipuncture, six-minute walk test, echocardiography, right heart catheterization, and cardiopulmonary exercise testing are part of the routine care for patients with PAH and will be familiar to all participants in the trial. Covid testing may be required prior to exercise testing and presents minimal risk and discomfort to most people. Procedures with a small, but extant risk of serious complications including right heart catheterization and cardiopulmonary exercise testing are optional sub-studies for this trial. These risks will be described and procedures will be done only in the setting of adequate staffing and resuscitation equipment to include at a minimum a registered nurse and cardiac catheterization technologist in the Catheterization Laboratory and a respiratory therapist or exercise physiologist in the Exercise Laboratory.

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). Adverse events will be collected and reviewed by a data safety monitoring board.

Pregnant women and prisoners are excluded from study.

2.3.2 POTENTIAL BENEFITS

Participants in this trial have the potential to benefit from the intervention. If the hypothesis is confirmed than participants using famotidine may experience fewer signs and symptoms of right heart failure over the course of the study. The proposed trial also has the potential to benefit the pulmonary arterial hypertension community at-large given the possibility that the REHAB-PH trial will identify a readily available medication that is the first of its kind to target right heart failure directly. Results from this trial could inform future trials that benefit the larger community of patients with a range diseases complicated by right heart failure (not related to PAH). Finally, results from the trial have the potential to benefit the health care system by providing a low cost adjunctive therapy for PAH patients, whose therapy currently represents a major expense for the health care system. These benefits may outweigh any risk associated with study procedures both for the study participant and the larger community.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine whether famotidine increases six-minute walk distance at 24 weeks in men and women with pulmonary arterial hypertension.	The primary end-point is the change in six-minute walk distance (6MWD) between baseline and 24 weeks. This will be compared between treatment groups.	The six-minute walk distance *i*s simple, reproducible, and well tolerated in patients with PAH. The 6MWD has been the primary outcome measure for the majority of pivotal trials of PAH therapeutics because of its relationship to hemodynamic parameters, treatment outcome, and survival.
Secondary		
To determine whether famotidine reduces BNP at 24 weeks To determine whether famotidine improves New York Heart Association (NYHA) functional class at 24 weeks To determine whether famotidine improves right ventricular morphology at 24 weeks including improved right ventricular dilation and TAPSE	Secondary endpoints include the change in BNP, NYHA functional class, right ventricular basal diameter, TAPSE, emPHasis-10 score, and the frequency with which routine therapies for patients with PAH are escalated during the trial.	Secondary outcomes were chosen to better understand the impact of the intervention on various aspects of the treatment response including health-related quality of life using disease specific validated tools.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To determine whether famotidine improves health related quality of life as estimated by the emPHasis-10 score To determine whether famotidine decreases the need to escalate PAH focused care (increased diuretics, escalating doses of pulmonary vasodilators, and/or adding an additional pulmonary vasodilator)		
Tertiary/Exploratory		
<u>Exercise sub-study:</u> To determine whether famotidine increases maximal oxygen uptake in individuals with pulmonary arterial hypertension at 24 weeks To explore changes in other metrics of the exercise response (oxygen uptake, Ve/VCO2 ratio, total achieved wattage) with famotidine relative to placebo over 24 weeks. <u>Right heart catheterization sub-study:</u> To determine whether famotidine increases stroke volume index at 24 weeks To explore whether famotidine is associated with differences in wedge pressure, right atrial pressure, and/or pulmonary vascular resistance at 24 weeks	The primary analyses will be the change in oxygen consumption (VO2) for the exercise sub-study and the change in stroke volume index (SVi) for the right heart catheterization sub-study conducted using the intent-to-treat (ITT) population. Qualitative descriptions of other exercise and hemodynamic markers including mean, median, and distribution will be presented stratified by treatment group.	While the two proposed sub-studies are powered to detect plausible, but large differences in exercise response or invasive hemodynamic markers, these studies are not powered to detect small to moderate differences. The co-primary intent of these sub-studies is to begin to understand appropriate end-points in trials of right heart targeted therapy. This more exploratory motivation is intended to complement but not supplant primary and secondary outcome measures.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study is a Phase II, single-center, blinded, randomized, placebo controlled trial designed to test whether famotidine improves functional capacity and metrics of right heart failure relative to placebo in participants with pulmonary arterial hypertension over 24 weeks. In addition, there are two sub-studies. One sub-study involves cardiopulmonary exercise testing and the other sub-study involves invasive hemodynamic evaluation using right heart catheterization.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The central aim of the proposed study is to determine whether famotidine improves right heart failure for participants with PAH. This includes the impact on functional outcomes (six-minute walk distance and CPET), patient-reported outcomes (emPHasis-10 questionnaire, Appendix 1), and metrics of right heart stress and strain (echocardiography, BNP, and invasive hemodynamics). Right heart failure is the key driver of morbidity and mortality for patients with PAH. Treatments for pulmonary vascular disease have been developed over the last twenty years; however, there are no cardiac-targeted therapies for this or any other form of right heart failure. Our work and the work of others strongly suggests that H2 receptor signaling is important in the pathogenesis and progression of heart failure and antagonism of the H2 receptor may improve the natural history of heart failure and pulmonary hypertension. The potential importance of this approach is augmented by the fact that famotidine is an extremely well-tolerated and inexpensive over-the-counter medication for gastro-esophageal reflux. Inexpensive and well-tolerated medications are important for all diseases; however, are particularly needed for patients with pulmonary vascular disease where current medications targeting the pulmonary vasculature are notable for their extreme expense and high side effect profile.

4.3 JUSTIFICATION FOR DOSE

Participants will receive either 20mg of famotidine or placebo and will take one tablet, once daily for 24 weeks. This dose was chosen because it is a standard clinically available dose resulting in effective antagonism of the H2 receptor. This dose was included in a previous observational study evaluating famotidine in heart failure with reduced ejection fraction.

Famotidine is widely available, inexpensive, and has relatively few side effects. This belies an intervention that is well tolerated with minimal impact on the health care system. If we show efficacy, this represents a high value addition for patients and society.

The choice of 24 weeks was not arbitrary. A previous randomized controlled trial showed that famotidine relative to an active control (teprenone) improved b-natriuretic peptide, left ventricular morphology, and New York Heart Association Functional Class over 24 weeks in participants with Heart Failure and Reduced Ejection Fraction (left heart failure).

To avoid contamination of the placebo arm by participants taking over-the-counter H2 receptor antagonists for acid reflux, we will provide all participants with a comprehensive list of H2 receptor antagonists to avoid during the trial. We will also provide Calcium Carbonate and Omeprazole for acute and chronic control of acid reflux symptoms during the trial. This will help to minimize inadvertent contamination of the control arm through self-treatment of acid reflux.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit shown in the Schedule of Activities (SoA), Section 1.3.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Male or female, age 18 to 80
2. WHO Group 1 Pulmonary Arterial Hypertension
3. NYHA Functional Class II, III, or IV at screening* (See Appendix 2 for Functional Class Decision Aid)
4. Stable dose of pulmonary vasodilators for 30 days prior to randomization
5. Right heart catheterization within five years demonstrating a mean pulmonary arterial pressure of ≥ 25 mmHg, an occlusion pressure of ≤ 15 mmHg, and a pulmonary vascular resistance of ≥ 3 wood units
    - Participants with a right heart catheterization within five years demonstrating a mean pulmonary arterial pressure of ≥ 25 mmHg and occlusion pressure of 15 - 20 mmHg will be considered for inclusion if the pulmonary vascular resistance ≥ 9 wood units and they are being treated with pulmonary arterial hypertension specific therapy
6. Able to walk with/without a walking aid for a distance of at least 50 meters

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Pregnant or lactating
2. Non-group 1 pulmonary hypertension or veno-occlusive disease
3. History of interstitial lung disease, unless subject has collagen vascular disease and has pulmonary function testing conducted within 12 months demonstrating a total lung capacity or vital capacity of ≥ 60 %
4. Has received or will receive an investigational drug, device, or study within 30 days or during the course of study
5. Left sided myocardial disease as evidenced by left ventricular ejection fraction < 40%
6. Any other clinically significant illness or abnormal laboratory values (measured during the Screening period) that, in the opinion of the Investigator, might put the subject at risk of harm during the study or might adversely affect the interpretation of the study data
7. Anticipated survival less than 1 year due to concomitant disease
8. Regularly taking an H2 receptor antagonist within 30 days of enrollment
9. Creatinine clearance of < 30 mL/min
10. History of bariatric surgery
11. Current treatment for HIV

Individuals with thrombocytopenia (<20,000/microliter), coagulopathy (INR >3), hyperkalemia (>6), hypokalemia (<2.5), or hyponatremia (125) cannot participate in the RHC sub-study. In addition, participants with known anatomic barriers to IJ placement, a latex allergy, or infection at the insertion site will be excluded from this sub-study.

Individuals with known, recent exercise associated syncope will be exclude from the cardiopulmonary exercise testing sub-study. In addition, individuals with recent myocardial infarction, unstable angina, uncontrolled arrhythmia, severe valvular stenosis, decompensated heart failure, active endocarditis, acute myocarditis or pericarditis, acute aortic dissection, or marked electrolyte abnormalities will be excluded from the CPET sub-study.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. This includes participants who undergo baseline studies, but who have not been randomized, and for whom the baseline evaluation inform clinical concern that they are not appropriate for the study as evidenced by meeting an exclusion criteria or failing to meet an inclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

All potential subjects for the REHAB-PH Trial will be recruited from the University of Washington Pulmonary Vascular Disease Program.

Potential participants seen in the UW Pulmonary Vascular Disease Clinic will be pre-screened using the electronic medical record. Potentially eligible participants will be recruited at the time of their clinic visit or if time permits, they will receive a one page letter via mail describing the study and/or a phone call from the study coordinator in anticipation of their next visit to clinic. During the potential participant's clinic visit, they will be approached and invited to participate in the REHAB-PH study by the study team at the UW Pulmonary Vascular Disease Clinic. A research coordinator will follow-up with any patient who is willing or considering participation in the study. This may include scheduling a baseline visit in-person at the clinic visit and/or following up by telephone.

Retention is a vital consideration for the success of the study. As we have done in other studies, we will maximize retention by careful training of clinical research staff on best practices for retaining participants. Staff conducting adherence and retention efforts will be trained to conduct effective informed consent to assure that participants fully understand the demands and nature of the study before they enroll. Clinical center staff will carefully review study requirements with the subjects, explain the concept of random assignment and what each treatment involves, and stress the importance of follow-up assessment even if they are not adhering to their assigned treatment. Participants will be nominally remunerated for their participation to offset travel and parking costs. Clinic staff will, at each visit, convey our appreciation for their participation in the study. Concerns about individual participants

will be raised with direct involvement, such as phone calls, by the PI and study center staff as needed to facilitate retention.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The study drug is Famotidine, a histamine H2-receptor antagonist. Participants will receive either 20mg of famotidine or placebo. H2 receptor antagonists are widely available, over-the-counter medications and acid reflux (their current indication) is common. Over-dose with an H2 receptor antagonists has not been described; however, to avoid contamination of the placebo arm by participants taking over-the-counter H2 receptor antagonists for acid reflux, we will provide all participants with a comprehensive list of H2 receptor antagonists to avoid during the trial. We will also provide Calcium Carbonate and Omeprazole for acute and chronic control of acid reflux symptoms during the trial. This will help to minimize inadvertent contamination of the control arm through self-treatment of acid reflux. We will employ adherence and retention principles and procedures that are standard in the cardiology trials unit at the University of Washington. In addition, the degree to which this approach is effective will be evaluated through a mass-spectrometry based assay for the presence of any H2 receptor antagonist in the blood of study participants at the end of the trial. Ideally H2 receptor antagonists will be seen in 100% of the assays in the active arm and 0% in the control arm. Significant deviation from this expected finding will be considered in the inference on results.

The placebo contains an inactive excipient powder and to preserve study blinding, the placebo tablets will be identical in size, shape, color, and appearance to the famotidine tablets.

Famotidine and matching placebo tablets will be in bottles containing 91 tablets. Following enrollment and randomization, each subject will receive one bottle to cover the first 12 weeks of the study, which will be subject-specific. The site staff will instruct the subject to take one tablet daily. At Week 12, subjects will receive another bottle to cover the last 12 weeks of the study.

6.1.2 DOSING AND ADMINISTRATION

Participants will be randomized to either take a placebo or a 20 mg tablet of famotidine, per oral, once a day for 24 weeks.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Harborview Medical Center Investigational Drug Services (HMC IDS) will distribute famotidine and placebo tablets for the University of Washington Medical Center Investigational Drug Services (UWMC IDS) to dispense. UWMC IDS will store the famotidine and placebo and dispense the pills to the study coordinator who will then give them to the subjects. The subjects will self-administer the pills at home

and bring any unused pills back to the study coordinator. Returned pills will be logged and then disposed of by UWMC IDS.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Kirkland Signature will manufacture Famotidine 20 mg tablets. HMC IDS will provide famotidine 20mg placebo capsules (Placebo) and over-encapsulation of famotidine 20 mg tablets (Famotidine) to the University of Washington Medical Center Investigational Drug Services (UWMC IDS). UWMC IDS will place the tablets in 91 count bottles and will label the bottles with blinded prescription labels prior to distribution.

6.2.3 PRODUCT STORAGE AND STABILITY

The bottles of famotidine and matching placebo should be stored at controlled room temperature of 15°C – 30°C (59°F – 86°F). Each bottle will have an expiration date.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Subjects will be randomly assigned in a 1:1 ratio to one of two arms using permuted block randomization: (1) placebo or (2) famotidine. Subject randomization will be stratified by NYHA/WHO Functional Class (NYHA/WHO Functional Class II versus Class III/IV) to ensure balanced representation of this important marker of severity. A randomization code will be computer-generated by contract research organization (CRO) Axio Research, LLC. Subjects meeting study entry criteria will be randomized via an interactive web response system (IWRS). The randomization schedule will be generated by the randomization statistician at Axio Research (who is not on the project team) or designee and maintained in a secure and limited-access location separate from the study investigator and members of the project team. The study subject, investigative staff, the Sponsor, the Sponsor study team (includes contractors and vendors), excluding the unblinded study site pharmacist will be blinded to treatment assignments during the study.

6.4 STUDY INTERVENTION COMPLIANCE

Study drug counts will be conducted at all study visits. Per protocol cohorts include 80% compliance with the once daily intervention. A total of 91 tablets will be provided at each study visit. A count of unused medications at the 12 and 24-week follow-up visit will be logged in a drug accountability log and used to determine compliance with the intervention.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

Participants are prohibited to take H2 receptor antagonists during the trial.

Research pharmacists will review the study participant's medications listed in their medical record and advise them about the timing of administration of their current medications with famotidine and the acid reflux concomitant medications provided. This will occur at the initial visit and as needed for any follow-up visits that have any new medications added between the visits.

According to pharmacokinetic analyses, single doses of famotidine 20mg raised intragastric pH to mean values of 5.0 (similar for when doses were given in the evening or after breakfast). There were no cumulative effects with repeated doses. However, there are many studies that have shown tachyphylaxis with repeated doses of H2RAs occurring after approximately a week of therapy. Repeated doses of H2RAs are associated with decreased time of gastric pH maintained above 4.0.

The impact on the availability of pulmonary vasodilators is as follows:

- Sildenafil: no interaction known; delayed rate of absorption with high-fat meals but not antacids (time delay 1 hr, reduced maximum concentration by 29%)
- Tadalafil: no significant interaction known; antacids reduced rates of absorption with no change in overall exposure; no significant effects observed with the co-administration of nizatidine 300mg
- Riociguat: no information available specifically with H2RAs; however, concurrent use with antacids is associated with up to 50% reduction in riociguat maximum serum concentration and 25% reduction in exposure; recommended to separate the administration of antacids and riociguat by at least 1 hr; specific mechanisms for these interactions are unknown but riociguat solubility is pH-dependent, and therefore, increases in gastric pH may be partially responsible
- Bosentan: no interaction
- Ambrisentan: no interaction
- Macitentan: no interaction
- Oral treprostinil: no interaction; bioavailability is increased by high fat, high calorie meals by up to 49% but not known to be impacted by acid suppression
- Selexipag: no interaction; time to peak concentration may be delayed with food but not known to be impacted by acid suppression.

References:
Famotidine [package insert]. Morgantown, WV: Mylan Pharmaceuticals Inc.; 2018.
McRorie JW, Kirby JA, Miner PB. Histamine2-receptor antagonists: rapid development of tachyphylaxis with repeat dosing. World J Gastrointest Pharmacol Ther. 2014; 5(2):57-62.
Adempas (riociguat) [package insert]. Whippany, MJ: Bayer HealthCare Pharmaceuticals Inc., 2013.
Interactions. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com. Accessed March 2019.

6.5.1 RESCUE MEDICINE

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Serious Adverse event(s) related to the trial medication
- Any relevant deterioration in the health of the subject (AEs, vital signs, laboratory parameters).
- Protocol violation
- Subject's inability to stay on the study drug or off other H2 blockers
- Subject withdrew consent

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF).

7.2 LOSS TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for a scheduled visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within a week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY AND SAFETY ASSESSMENTS

At the baseline visit participants will be consented and inclusion and exclusion criteria will be assessed for eligibility. Participants will then undergo a standardized clinical assessment with medical history, symptom assessment including NYHA functional class, vital signs (includes height, blood pressure, heart rate, oxygen saturation), weight, and physical examination. Demographics will be collected. A blood draw will include safety laboratories including comprehensive metabolic panel, complete blood count, BNP, and pregnancy test (for pre-menopausal women). The pregnancy test can be performed as either a blood or urine test. A blood-based pregnancy test is preferred; however, if a urine test is used then it must be performed by study personnel and documented in the medical record. All participants will have serum collected for mass-spectrometry at the end of the study to evaluate for contamination of the study design by individuals taking over-the-counter H2 receptor antagonists. Serum, plasma, and blood

for RNA isolation will be collected and stored for participants. Subjects will have an option to opt-out of this additional research blood sample. All participants will have a transthoracic (TTE) echocardiogram and emPHasis-10 measure of health-related quality of life. They will also complete a 6 minute walk distance (6MWD) at their baseline visit. Distance, BORG dyspnea scores, peak heart rate, oxygen saturation, and heart rate recovery at one minute will be collected to characterize the walk.

Participants who are not participating in the right heart catheterization or exercise sub-studies will be randomized and study drug will be dispensed at this visit. Participants will be instructed to take one tablet daily (20 mg of famotidine or placebo) the following day which will represent day zero and entry into the study. An antacid (Calcium Carbonate) and proton pump inhibitor (Omeprazole), both over-the-counter medications, will be provided by a study physician to participants as needed for short and long term heartburn control in an effort to try and minimize contamination of the study question by inadvertent H2 receptor antagonist use by participants attempting to self-treat heartburn with over-the-counter medications.

Individuals who are participating in the right heart catheterization or exercise sub-studies will be randomized and study drug will be dispensed at their last baseline study assessment. These participants will also be instructed to take one tablet daily (20mg of famotidine or placebo) the day following randomization and dispensing of the study drug.

Regardless of the participation in sub-studies, all baseline assessments need to be completed within 14 days prior to the start of study drug (not inclusive of the date the first dose of study drug is taken). The day study drug is taken will be considered day 0.

Week 4 phone call will be on day 28 ± 7. This visit will address study drug adherence and adverse events.

Week 12 visit will occur at day 84 ± 7. This visit will include a standard clinical assessment with a symptom assessment including NYHA Functional Class, vital signs, weight, and physical examination. Participants will also have a 6-minute walk distance, emPHasis-10 score, evaluation for adverse events, evaluation for medication and study drug compliance, and dispensation of study drug. Due to the COVID-19 pandemic, this visit can be done as telehealth or in-person based on current COVID-19 levels in the community and patient preference. If visit is done as telehealth it will include a symptom assessment including NYHA Functional Class, emPHasis-10 score, evaluation for adverse events, and evaluation for medication and study drug compliance. The UWMC Investigational Drug Service will ship the next supply of study medication to the subject via FedEx overnight shipping to coincide with this visit. In person visits will be encouraged.

Week 24 visit will occur at day 168 ± 7 and will include all components included in the baseline visit: a standard clinical assessment with a symptom assessment including NYHA Functional Class, vital signs, weight, and physical examination. Participants will also have a 6-minute walk distance, an echocardiogram, emPHasis-10, evaluation for adverse events, evaluation for medication and study drug compliance, and a blood draw including a comprehensive metabolic panel, complete blood count, BNP,

and pregnancy test if indicated. The pregnancy test can be performed as either a blood or urine test. A blood-based pregnancy test is preferred; however, if a urine test is used then it must be performed by study personnel and documented in the medical record. All participants will have serum collected for mass-spectrometry at the end of the study to evaluate for contamination of the study question by individuals taking over-the-counter H2 receptor antagonists. Serum, plasma, and blood for RNA isolation will be collected and stored for participants.

Adverse events and concomitant medications will be assessed and collected at all visits.

Optional Right Heart Catheterization (RHC) Evaluation: Subjects will have the option to take part in the RHC portion of the study that will be performed within 14 days of the 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. This is a procedure which is performed for all patients with PAH. The purpose of this optional evaluation is to track changes in the measurements of the subjects' heart and lungs that might be related to study treatment with famotidine. 1% lidocaine local anesthesia will be used. It will take 3-4 hours to complete the right heart catheterization. On the day of the right heart catheterization, subjects will check into the cardiac catheterization laboratory at the University of Washington Medical Center. A nurse will check the subject's vital signs and basic bloodwork to make sure that the procedure is safe to perform. Once this is done, subjects 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 the neck. After numbing the area, Dr. Leary will place a catheter into a vein, the right atria, right ventricle, and pulmonary artery and measure pressures at each position and check to see how much blood the heart is pumping. The process of inserting the catheter and taking measurements normally takes approximately 20-30 minutes. After these measurements, the catheter will be removed, a nurse will hold pressure on the area to ensure that there is no bleeding, and the subject will then be free to go.

Optional Cardiopulmonary Exercise Test (CPET) Evaluation: Subjects will have the option to take part in the CPET portion of the study that will be performed within 14 days of the 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. CPET 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 is not routinely done for all individuals with PAH. This test measures how the body tolerates physical activity. Due to the Covid 19 Pandemic, the Lung Function Testing department at UWMC is requiring Covid 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, subjects will check into the Lung Function Testing Center at the University of Washington Medical Center. They should wear clothing suitable for exercise. A respiratory therapist will

check the subject's vital signs and conduct breathing tests. After this they will hook up an EKG, monitor the subject's oxygen via a probe on their finger, and place a neoprene mask over their nose and mouth. These will measure a number of important exercise characteristics. Subjects will then ride a stationary bicycle in the exercise lab. The test is variable in length and designed to push the subject to exercise as hard as they 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 the subject is done, a respiratory therapist will continue to monitor the subject for 5-10 minutes at rest. After this time, subjects will be free to go.

Participants in the invasive hemodynamic and cardiopulmonary exercise testing (CPET) sub-studies will have the option to do both tests on the same day or separate days, but within the 3 days of the final visit.

8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.2.1 DEFINITION OF ADVERSE EVENTS (AE)

Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure.

8.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Any AE that results in any of the following outcomes:

- Death
- Life-threatening
- Event requiring inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity

8.2.3 CLASSIFICATION OF AN ADVERSE EVENT

8.2.3.1 SEVERITY OF EVENT

AEs are graded according to the following scale:

Mild: An experience that is transient, & requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. This includes transient laboratory test alterations.

Moderate: An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes laboratory test alterations indicating injury, but without long-term risk.

Severe: An experience that requires therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment it becomes an SAE.

8.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

The study uses the following AE attribution scale:

Definite: AE is clearly related to study drug or a study procedure
Probable: AE is likely related to study drug or a study procedure
Possible: AE is possibly related to study drug or a study procedure
Unlikely: AE is doubtfully related to study drug or a study procedure
Unrelated: AE is clearly not related to study drug or a study procedure

8.2.3.3 EXPECTEDNESS

Expected AEs associated with famotidine include:
Headaches

Although expected AEs associated with right heart catheterization are uncommon, they include: Pain/discomfort, nausea, vomiting, redness, irritation, bruising, or development of a small hematoma/bleeding, allergic reactions in rare instances (e.g. hives or difficulty breathing from lidocaine or catheters), infection, damage to nearby structures (artery, vein, nerve, lung), hypertensive crisis, hypotension, chest pain, bronchospasm, arrhythmia, dizziness/syncope, or death (Hoeper et al., Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers, J Am Coll Cardiol; 48: 2546-52, 2006).

Although expected AEs associated with exercise testing are uncommon, they include:
Changes in blood pressure and heart rate, fatigue, discomfort, musculoskeletal injury, syncope, arrhythmia, heart attack, or stroke (Skalski et al. The safety of cardiopulmonary exercise testing in a population with high-risk cardiovascular diseases, Circulation; 126:2465-72, 2012).

Expected AEs associated with the underlying natural history of pulmonary arterial hypertension or PAH therapies over a 24-week study include:
Dizziness, syncope, leg swelling, abdominal swelling, chest pain, shortness of breath, hypoxemia, hemoptysis, nausea, vomiting, diarrhea, jaw pain, flushing, joint pain, muscle pain, infection, arrhythmia, heart failure, pericardial effusion/tamponade, cirrhosis, thrombosis or embolus, stroke, cardiac arrest, or sudden cardiac death.

8.2.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The study team will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 14 days (for SAEs) after the last day of study participation. AEs are identified at any of the three in-person visits, during a phone visit, during a study-based procedure (e.g. heart catheterization or cardiopulmonary exercise test) or when notified outside of the normal visit structure by a participant or surrogate. Events will be followed until resolution or stabilization.

8.2.5 ADVERSE EVENT REPORTING

Deaths and unexpected, but definite, probable, or possibly-related SAEs are reported to the PI and DSMB within 48 hours through the use of an e-mail transmitted SAE report form copied to the PI, executive secretary of the DSMB, and DSMB Chair.

In addition, all events that meet the definition of an unanticipated problem (in the PI's opinion) should be reported to the UW IRB within 10 days using the Zipline Online portal.

An unanticipated problem is a problem or event that meets **all** of the following criteria:

- Unexpected – The harm (or potential harm) is inconsistent with risk information previously reviewed and approved by the Institutional Review Board (IRB) in terms of nature, severity, or frequency as well as the characteristics of the study population.
- Related or probably related to participation in the research;
    - Probably related: There is a reasonable probability (more likely than not) that the incident, experience or outcome may have been caused by the procedures involved in the research, or that it is associated with the use of any drug, biologic, or medical device that is part of the research.
- Suggests that the research places (or did place) one or more subjects or others at a greater risk of harm than was previously known or recognized. This includes physical, psychological, economic, educational advancement, or social harm.

Reports are required within 24 hours for qualifying medical problems covered by the UW Human Subjects Assistance Program (HSAP), a breach of confidentiality, or inappropriate use of protected health information.

In addition, the IRB requires a report within 10 days for serious non-compliance, continuing non-compliance (serious or non-serious), emergency deviation from IRB approved procedures to eliminate an apparent hazard to subjects or others, complaints that cannot be resolved by the research team, audit notification from a federal agency, information that indicates a new potential risk (e.g. new publication), and all DSMB reports.

Expected S(AE)s are not required to be reported to the UW IRB outside of continuing review.

8.2.6 REPORTING EVENTS TO PARTICIPANTS

Participants will be updated with any learned information during the study that may affect their willingness to participate.

8.2.7 EVENTS OF SPECIAL INTEREST

Not applicable.

8.2.8 REPORTING OF PREGNANCY

Pregnancy and the post-partum period is a highly dangerous and volatile time for women with pulmonary arterial hypertension and as a result participants who are pregnant, lactating, or have

evidence of dynamic disease with pulmonary vasodilator adjustment within 30 days of randomization will not be included. It is also possible that harmful side effects that are not yet known could happen to both the mother and unborn or breast-feeding child.

The investigator must be notified immediately if the subject becomes pregnant and they will be withdrawn from the study. This is anticipated to occur uncommonly if ever. The clear clinical recommendation in pulmonary arterial hypertension is dual-method contraception and the risk of death with pregnancy is prohibitive. Unintended or intended pregnancy is a very rare event in the pulmonary vascular disease clinic.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Efficacy Endpoint(s): The primary endpoint is the difference in 6-minute walk distance.

Secondary Efficacy Endpoint(s): The secondary endpoint is the difference between treatment groups in BNP, NYHA functional class, TAPSE, right ventricular basal diameter, emPHasis-10 score, and number of participants with an escalation of routine clinical treatments for PAH for each visit.

We hypothesize that famotidine use in individuals with PAH will improve 6-minute walk distance over 24 weeks relative to placebo.

We further hypothesize that over 24 weeks famotidine use in individuals with PAH will lower BNP, improve the NYHA functional class, increase the TAPSE, diminish the right ventricular basal diameter, improve the emPHasis-10 score, and minimize the need to escalate routine treatment for PAH (diuretics and pulmonary vasodilators).

9.2 SAMPLE SIZE DETERMINATION

The primary endpoint is the change in six-minute walk distance. The study was powered to detect a difference of 31.9 meters. A 31.9 meter improvement in 6MWD is well aligned with established thresholds for a minimally important difference in patient reported outcomes. The 6MWD was chosen because 6MWD is a surrogate for patient-centered outcomes and was the primary endpoint in labeling trials for most of the medications used to treat pulmonary arterial hypertension (PAH).

The field is appropriately shifting toward larger event driven trials; however, we did not feel a larger event driven trial of famotidine was warranted at this juncture. The current proposal is the first randomized evaluation of this drug and this pathway in individuals with right heart failure and/or PAH and a smaller Phase II trial was felt to be a more appropriate next step.

For the RHC sub-study, the initial sample size was set at 10 participants based on the following power to detect large differences.

Size of difference	SV index (mL/m2)	Total sample size	n per group	power
Large	20	10	5	0.87
Medium-high	15	10	5	0.67
Medium-low	10	10	5	0.36
Small	5	10	5	0.13

As the study progressed, recruitment into this invasive arm appeared to be more feasible and the sample size was increased to 20 participants.

Size of difference	SV index (mL/m2)	Total sample size	n per group	power
Large	20	20	10	0.99
Medium-high	15	20	10	0.95
Medium-low	10	20	10	0.68
Small	5	20	10	0.23

9.3 POPULATIONS FOR ANALYSES

Intent-to-Treat Population: All subjects who are randomized will comprise the intent-to-treat (ITT) population. The ITT population will be analyzed for the primary and secondary endpoint analyses and will comprise the safety population used for all safety analyses.

Per Protocol Population: Subjects in the ITT population whose famotidine medication reconciliation suggest adherence to study drug for 80% or more of administered doses will be evaluated as the per protocol population. The per-protocol population will be used in the sensitivity analyses of the primary and secondary endpoints. A second per protocol population will include participants for whom H_2 receptor antagonists are detected by Mass Spectrometry at the final visit relative to those for whom H_2 receptor antagonists are not detected.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Except where otherwise noted, all tests will be two-sided and statistical significance will be determined at the 0.05 level.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary endpoint is the difference between treatment groups in the change of 6-minute walk distance (6MWD) between baseline and 24 weeks. Linear regression will be performed with the change in 6MWD between baseline and 24 weeks as outcome and treatment group as the primary predictor of interest, adjusted for baseline 6MWD and baseline NYHA functional class as the stratification variable. The estimate of the treatment effect will be provided with associated 95% confidence interval (CI).

Missing 6MWD at 24 weeks will be imputed as follows. Subjects known to be dead before the 24 week assessment will have zero imputed for their 24 week 6MWD. Missing 24 week 6MWD for subjects who are alive will be imputed using multiple imputation. The imputation model will have prognostic variables as the predictor variables. Prognostic variables will include age, gender, and etiology of pulmonary hypertension, baseline six minute walk test, baseline right ventricular diameter, and baseline BNP. The multiple imputation will use Markov Chain Monte Carlo (MCMC), which assumes that the variables in the imputation model have a joint multivariate normal distribution (MVN). The number of imputations to be performed will be 100. One hundred is selected because it is not too large that it requires heavy computations and is not too small (such that the Monte Carlo error is still small enough at around 0.1 times the standard deviation). The “proc mi” procedure in SAS will be used to impute the missing observations.

Although every effort will be made to avoid missing data, a range of approaches to missing 6MWD will be considered as sensitivity analyses representing a range of conservative and anti-conservative biases to describe the range of possible differences.

<u>Sensitivity Analyses of the Primary Endpoint</u>
Sensitivity analyses of the primary endpoint will include:

- a linear regression model using a worst case scenario (WCS) method of imputation
- a linear regression model of the 24 week 6MWD without imputation (complete case analysis)

(1) The worst case scenario method of imputation will impute zero for all missing 6MWD at week 24.
(2) The linear regression method will model the 24 week 6MWD on treatment assignment, adjusting for baseline 6MWD and baseline NYHA class using least squares and robust standard error estimates. For all methods, treatment effect estimates and 95% CIs will be presented.

Additional Analyses of the Primary Endpoint
Additional analyses of the relative change in 6MWD will include the proportion of participants who achieve a minimally important change in 6MWD of 31.9 meters or greater. To test the null hypothesis that there is no difference between the treatment groups, logistic regression adjusted for the NHYA functional class (stratification variable) will be used. The difference between treatment groups will be provided with associated 95% CI. Subjects missing the 24 week 6MWD will not be counted as having achieved a minimally important change.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Summary statistics (mean, standard deviation, median and range) of BNP (untransformed and log-transformed), NYHA functional class, right heart strain, TAPSE, right ventricular basal diameter, emPHasis-10 score, and number of participants with an escalation of routine clinical treatments for PAH for each visit will be presented by treatment group. Change in these parameters (log-transformed value for BNP) will be evaluated between the treatment groups using linear regression adjusted for the value at baseline and NYHA functional class (stratification variable). The difference with 95% CIs will be reported.

The BNP is expected to vary by NYHA functional class. An additional sensitivity analysis will be performed with the difference of log-transformed BNP between baseline and week 24 as the outcome, with the predictor variables being baseline log-transformed BNP, treatment group, baseline NYHA functional class, and an interaction term between treatment group and baseline NYHA functional class.

Missing data in the secondary outcomes will be imputed in an analogous fashion to the primary outcome including sensitivity analyses to define the range of uncertainty imposed by missing data (worst case scenario and complete case analysis). The worst case scenario is different by variable. BNP and right ventricular basal diameter will be set to the highest value in the observed population. TAPSE will be assumed to be zero, emPHasis-10 score will be assumed to be 50, NYHA functional class will be assumed to be IV, and a participant will be assumed to have escalated PAH specific care.

9.4.4 SAFETY ANALYSES

All reported (S)AEs will be coded using MedDRA and grouped by body system. (S)AEs will be tabulated by treatment group using standard coding terms. Incidence of AEs by treatment arm will be tabulated by seriousness, severity, and relationship to study drug. If an AE is reported more than once for a given subject, the greatest severity and the worst-case relationship will be presented in tables. The number of SAEs and AEs will be summarized for each treatment group as follows: (i) The proportion of subjects with at least one (S)AE, (ii) The average number of (S)AEs per subject, and (iii) The rate of (S)AEs per

subject week of follow-up. Histograms showing the frequency of the number of (S)AEs in each treatment group will be included. Rates of (S)AEs by System Organ Class (SOC) will be presented by treatment group. Poisson regression modeling will be used to derive rate ratios and 95% CIs for each SOC. Rate ratios will be compared using a two-sided 0.05 level test for Poisson count data.

Safety lab data at each study visit and changes from baseline will be summarized by treatment group. In addition, clinical laboratory summaries will be presented by treatment group including: (i) incidence of significant abnormalities by visit; (ii) tables summarizing the frequencies of subjects below, within, and above the normal reference ranges at baseline and end of study; and (iii) tables displaying baseline to end of study shifts in each laboratory value (shifts between below, within or above normal range).

Although drug discontinuation is anticipated to be infrequent, the proportion of subjects permanently discontinuing study drug will be tabulated by treatment group. Drug discontinuation events will be categorized as: (1) Permanently discontinued study drug and (2) Permanently discontinued study drug and withdrew from study. The reason for permanent drug discontinuation will be summarized. The number of hospitalization events and proportion of subjects hospitalized from baseline to study termination will be summarized and compared by treatment group. Poisson regression modeling will be used to derive rate ratios and 95% CIs to compare hospitalization rates between treatment groups.

9.4.5 DEMOGRAPHIC AND BASELINE DESCRIPTIVE STATISTICS

Treatment groups will be described and compared with respect to baseline demographic and clinical characteristics such as age, gender, race, ethnicity, height, weight, body mass index, use of concomitant medications, and markers of pulmonary hypertension disease severity (e.g., right ventricular structure and function, BNP, 6-minute walk distance, New York Heart Association (NYHA) functional class). Continuous measures will be analyzed using t-tests and categorical variables will be analyzed using chi-square, Fisher's exact, or Cochran-Mantel-Haenszel tests.

9.4.6 DSMB REVIEW OF ONGOING DATA

Reports to the DSMB will focus on trial integrity (recruitment, protocol deviations/violations, completeness of follow-up and adherence) and safety. Comprehensive safety interim reports will be provided semi-annually to the DSMB. Comprehensive, safety reports will include detailed summaries of all SAEs, AEs, laboratory parameter listings, drug discontinuations and withdrawals as well as other pertinent safety data. The DSMB will recommend continuation or discontinuation of the study based on these interim reviews. Because of the length, size, and scope of the proposed study interim analyses for efficacy or futility will not be performed.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to administering study intervention.

All participants will be given a list of H2 receptor antagonists to avoid during the trial.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. A study team member will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will be given adequate opportunity to consider all options by allowing subjects to take the consent form home and to contact the study team at a later time if they would like to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. Study-specific procedures (like right heart catheterization) may be scheduled but not performed before consent is obtained. Many of the study endpoints including the six-minute walk distance, BNP, NYHA functional class, and echocardiogram are also part of routine clinical care. As such clinically obtained testing within the specified time window may be used as part of the baseline research assessment. Because these tests are not "study-specific" it is not considered a violation if they are obtained before consent is obtained. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator

(PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

Authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and the U.S. Food and Drug Administration (FDA) may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Axio Research. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by Axio Research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Axio Research.

Certificate of Confidentiality

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative,

or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at Axio Research. After the study is completed, the de-identified, archived data will be transmitted to and stored at the University of Washington, for use by other researchers including those outside of the study. Permission to transmit data to the National Institute of Health (NIH) data banks will be included in the informed consent.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the University of Washington with the same goal as the sharing of data with the NIH data banks. A transcript wide analysis of RNA samples may be performed. These samples could be used for future studies on any topic related to pulmonary vascular disease or right heart failure. The NIH will be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed and data has been submitted to the NIH data banks.

When the study is completed, access to study data and/or samples will be provided through the University of Washington.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
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10.1.6 SAFETY OVERSIGHT

Primary safety oversight will be performed by the Principal Investigator and Study Co-Investigators. Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including a pulmonary hypertension specialist, a statistician, ethics specialist, cardiovascular specialist, and clinical trials specialist. Members of the DSMB should be

independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to National Institutes of Health staff. All changes to the protocol or consent will be submitted to the NHLBI and DSMB for review prior to submission to the IRB or execution in the study.

10.1.7 CLINICAL MONITORING

Not applicable.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The sole clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site for clarification/resolution.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of auditing and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the International Business Machines (IBM) Clinical Development database system provided by Axio Research. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 6 years after study closure.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or International Conference on Harmonization Good Clinical Practice (ICH GCP). The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents and entered into the IBM Clinical Development system. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers after the completion of the primary endpoint by contacting the University of Washington.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include transcriptomic, RNA sequencing data.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Heart, Lung, and Blood Institute (NHLBI) has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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12 APPENDIX 1: EMPHASIS-10 QUESTIONNAIRE

emPHasis10

Date:

Subject ID:

This questionnaire is designed to determine how pulmonary hypertension (PH) affects your life. Please answer every question by placing a tick over the ONE NUMBER that best describes your recent experience of living with PH.

For each item below, place a tick (✓) in the box that best describes your experience.

I am not frustrated by my breathlessness	0 1 2 3 4 5	I am very frustrated by my breathlessness
Being breathless never interrupts my conversations	0 1 2 3 4 5	Being breathless always interrupts my conversations
I do not need to rest during the day	0 1 2 3 4 5	I always need to rest during the day
I do not feel exhausted	0 1 2 3 4 5	I always feel exhausted
I have lots of energy	0 1 2 3 4 5	I have no energy at all
When I walk up one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up one flight of stairs I am very breathless
I am confident out in public places/crowds despite my PH	0 1 2 3 4 5	I am not confident at all in public places/crowds because of my PH
PH does not control my life	0 1 2 3 4 5	PH completely controls my life
I am independent	0 1 2 3 4 5	I am completely dependent
I never feel like a burden	0 1 2 3 4 5	I always feel like a burden

Total:

Date:

pha UK
pulmonary hypertension association

MANCHESTER 1824
The University of Manchester

13 APPENDIX 2: FUNCTIONAL CLASS DECISION AID

Functional Class Decision Aid

Does the patient have symptoms most likely related to pulmonary hypertension:

1. At rest?	yes ☐	no ☐	n/a ☐	
2. When getting up or dressing?	yes ☐	no ☐	n/a ☐	
3. When washing, brushing teeth or having a shower?	yes ☐	no ☐	n/a ☐	
4. When walking around in the house?	yes ☐	no ☐	n/a ☐	
5. When walking on level ground at slow speed?	yes ☐	no ☐	n/a ☐	FC IV

6. When climbing up to 2 flights of stairs at reduced (slow) speed?	yes ☐	no ☐	n/a ☐	
7. When walking on level ground at normal (pedestrian) speed?	yes ☐	no ☐	n/a ☐	FC III

8. When climbing 2 or more flights of stairs at normal speed?	yes ☐	no ☐	n/a ☐	
9. When walking uphill?	yes ☐	no ☐	n/a ☐	FC II

10. When performing vigorous physical activity?	yes ☐	no ☐	n/a ☐	FC I

Investigator Determined Functional class for this patient: WHO FC ☐