Protocol REHAB-PH

Repurposing a histamine antagonist to benefit patients with pulmonary hypertension

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Phase:	2
Methodology:	Single-center, randomized, double-blinded, placebo controlled, parallel design
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SIGNATURE PAGE

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Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance's and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

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1.00			Original document	

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ABBREVIATIONS

Abbreviation	Definition
6MWD	Six-minute walk distance
AE	Adverse event
ATC	Anatomic Therapeutic Class
BNP	Brain natriuretic peptide 32
CMH	Cochran-Mantel-Haenszel
CPET	Cardiopulmonary exercise testing
CRO	Contract research organization
CSR	Clinical study report
DSMB	Data and safety monitoring board
ECG	Electrocardiogram
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICEs	Intercurrent events
ICH	International Council on Harmonization
IWRS	Interactive web response system
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MVN	Multivariate normal distribution
PAH	Pulmonary arterial hypertension
PK	Pharmacokinetic
PPS	Per Protocol Set
PT	Preferred Term
RHC	Right heart catheterization
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SOC	System Organ Class
TAPSE	Tricuspid Annular Plane of Systolic Excursion
TEAE	Treatment-emergent adverse event
WCS	Worst case scenario

1 INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1 Introduction

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data to answer the study objective(s). The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

1.2 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 dilation 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)

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.

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

2 STUDY DESIGN

2.1 Introduction

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.

This study is a Phase II, single-center, double-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.

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 will be randomized to receive placebo or famotidine, 20 mg daily, per oral, and will be assessed for efficacy and safety for 24 weeks as described in the Schedule of Assessments of the protocol. The Schedule of Assessments is provided in Table 9-1, further details are available in the study protocol.

The study will consist of the following periods:

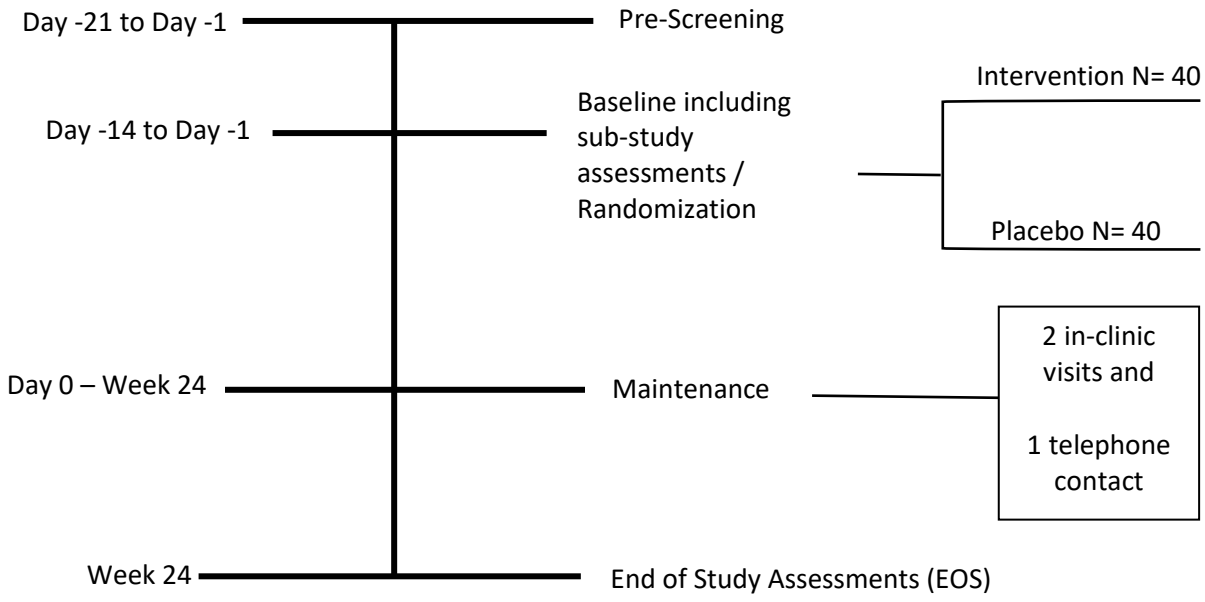
- Screening period: up to 21 days
- Treatment period: up to 24 weeks

The study design is shown in Figure 2-1.

There are two sub-studies proposed for this trial. One sub-study involves cardiopulmonary exercise testing (CPET) and the other sub-study involves invasive hemodynamic evaluation using right heart catheterization (RHC). 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. Exercise response and invasive hemodynamic differences in participants with pulmonary hypertension with and without exposure to famotidine will be studied.

Figure 2-1: Study design



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.

2.2 Randomization Methodology

A total of 80 subjects are to 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.

2.3 Stopping Rules

Not applicable, see Section 2.5.

2.4 Blinding

This is a double-blind study in which all participants, Investigators, and study personnel involved in the conduct of the study, including data management, are blinded to treatment assignment except for:

- An unblinded independent statistician or designee who will prepare and have access to the randomization code
- The unblinded pharmacist at study site

Although unblinded to treatment assignment, none of the above roles will have access to unblinded summaries of efficacy or safety data.

The following personnel will have access to unblinded efficacy and safety data in order to discharge their roles for data analysis and periodic safety review meetings:

- The unblinded statistical programming team and independent DSMB support statistician who will prepare the unblinded reports for review

Other than the above-mentioned personnel, all other individuals involved in the study conduct, statistical analysis and reporting will remain blinded until the after official study unblinding at the end of the study. The DSMB will review masked data by treatment arm with the option to unmask during the meeting. One DSMB member asking for unmasking is sufficient for unmasking of the DSMB to occur. The DSMB also has the option to unmask only for a single individual safety event (e.g., a death).

2.5 Interim Analyses

Reports to the Data and Safety Monitoring Board (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.

3 STUDY ENDPOINTS

3.1 Efficacy Variables

The study objectives and efficacy endpoints are summarized in Table 3-1.

Table 3-1: Study 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 endpoint 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 To determine whether famotidine improves health related quality of	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.

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 FAS. 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.

3.2 Pharmacokinetic Variables

Not applicable.

3.3 Safety Variables

Safety assessments performed during the study included physical examinations, measurement of vital signs (includes height, blood pressure, heart rate, oxygen saturation), weight, symptom assessment, clinical laboratory evaluations including comprehensive metabolic panel, complete blood count, pregnancy test (if premenopausal), and monitoring of adverse events.

4 ANALYSIS SETS

4.1 Analysis Set Definitions

The following Analysis sets will be evaluated and used for presentation and analysis of the data:

- ***Screening Analysis Set:*** Includes all subjects who signed the informed consent form.
- ***Enrolled Analysis Set:*** Includes all subjects in the Screening Analysis Set who were assigned a randomized treatment.
- ***Full Analysis Set (FAS)****:* Includes all randomized subjects who received at least 1 dose of study medication. Subjects will be analyzed according to their randomized treatment.
- ***Per Protocol (PP) Set 1 (PPS1)****:* Includes all subjects in the FAS whose famotidine medication reconciliation suggest adherence to study drug for 80% or more of administered doses. Subjects will be analyzed according to their randomized treatment.
- ***Per Protocol (PP) Set 2 (PPS2)****:* Includes all subjects in the FAS who (1) were randomized to famotidine for whom H_2 receptor antagonists are detected by mass spectrometry at the final visit and (2) those randomized to placebo for whom H_2 receptor antagonists are not detected at the final visit. Subjects will be analyzed according to their randomized treatment.
- ***Safety Analysis Set (SAF)****:* Includes all randomized subjects who received at least 1 dose of study medication. Subjects will be analyzed according to their actual treatment. Actual treatment is defined as the treatment received for most of the days during the treatment phase of the study.

Per ICH-E9 [1] and ICH-E9-R1 [2] guidelines, will use FAS instead of intention-to-treat. The FAS will be the primary analysis set for the analysis of the primary and secondary efficacy endpoints.

The PPS1 and PPS2 will be used in the sensitivity analyses of the primary and secondary efficacy endpoints.

The SAF will be the primary set for the analysis of the safety parameters.

4.2 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or International Council 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.

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.

All protocol deviations will be listed.

5 DATA HANDLING

5.1 Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.4 or later), unless otherwise noted. Medical comorbidities and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or later. Prior and concomitant medications will be coded using World Health Organization (WHO) Drug version Global B3 (March 2021 or later). The actual version of the dictionary used will be noted in the footnote of the respective output.

5.2 Data Conventions

The following conventions will be used:

- **Period definition:**
  - **Screening Period:** The period prior to the date of first dose of study drug (Day 0)
  - **On-Treatment Period:** The period from date of first dose of study drug through the Week 24 study visit
- **Study day 0:** The date of first dose of study drug
- **End of Treatment Visit:** End of treatment/early withdrawal visit
- **End of Study Visit:** The last recorded visit date
- **Unscheduled or repeated visits:** Unscheduled visits results will be listed, but not included in tables or graphs.
- **Conversion factors:**
  - 1 month = 30.4375 days
  - 1 year = 365.25 days
  - 1 week = 7 days
  - °C = (°F - 32)/1.8
- **Additional rules**
  - Age (years) = (date of informed consent – date of birth + 1) / 365.25, rounded to the lowest whole number.
  - Weight values recorded in pounds will be converted to kilograms using the following formula: kilograms = pounds/2.2046.
  - Height values recorded in inches will be converted to centimeters using the following formula: centimeters = inches*2.54.

- Duration on study (weeks) = (Last visit date – randomization date + 1) / 7.
- Duration on treatment (weeks) = (Last study drug intake date – first study drug intake date + 1) / 7.
- (Absolute) Change from baseline = Value at the time point – Baseline value.
- Relative change from baseline = [(Value at the time point – Baseline value) / Baseline value] x 100.

5.3 Methods of Pooling Data

Not applicable.

5.4 Withdrawals, Dropouts, Loss to Follow-up

Discontinued subjects will not be replaced whether they received or did not receive the study drug. The multiple imputation approach is included in Section 6.4.

Follow-up of subjects who discontinued the study drug early will continue until Week 24 and the study procedures will be assessed as per the schedule of assessment (see Table 9-1).

5.5 Visit Windows

All visits (scheduled, unscheduled or withdrawal) will be mapped to an analysis visit as defined in Table 5-1, where Day 0 is defined as the date of first dose of study treatment. All safety and efficacy analyses will be based on the analysis visit. In cases where a subject has more than one particular analysis visit, the visit with non-missing data closest to the protocolled visit will be selected for analysis.

Table 5-1: Evaluation Intervals for Efficacy Analysis

Scheduled Visit	Protocol-Specified Interval	Interval for Analysis Visit
Baseline	Day –14 to Day –1	Day –14 to Day -1
Week 12	Day 77 to Day 91	Day 0 to Day 125
Week 24	Day 161 to Day 175	Day 126 to Day 175

6 STATISTICAL METHODS

6.1 Sample Size Justification

The primary endpoint is the change in six-minute walk distance (6MWD). 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 (Mathai SC, et al. Am J Respir Crit Care Med, 2012; 186(5):428-433). The 6MWD was chosen because it 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).

Standard deviation in 6MWD among PAH participants with NYHA functional class II, III, or IV symptoms is 37.6 meters (national Pulmonary Hypertension Association Registry; unpublished data). As shown, the proposed sample size has adequate power (0.96) to detect a minimally important different in 6MWD even with 10% attrition in the study sample (power, 0.94).

Table 6-1: Power to detect a minimally important difference in 6MWD (31.9 meters)

Alpha	Sample size per group	Power for the total sample size	Sample size per group with ~10% attrition	Power with attrition
0.05	20	0.74	18	0.69
0.05	40	0.96	36	0.94
0.05	60	0.99	54	0.99

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

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

Size of difference	VO2 (mL/min/kg)	Total sample size	n per group	power
Large	8	10	5	0.96
Medium	4	10	5	0.46
Low	2	10	5	0.15

6.2 General Statistical Methods

6.2.1 General Methods

All outputs will be incorporated into Microsoft Excel or Word files, sorted and labeled according to the International Conference on Harmonization (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy and safety parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the mean, median, standard deviation, minimum and maximum values will be presented.

Formal statistical hypothesis testing will be performed with all tests conducted at the 2-sided, 0.05 level of significance. Summary statistics will be presented, as well as 95% confidence intervals on selected parameters, as described in the sections below.

6.2.2 Definition of Baseline

Baseline is defined as the last non-missing assessment prior to the first dose of study treatment. On the day of randomization all participants 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 day following randomization and dispensing of the study drug. 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. See Section 5.5 for details of the visit window for baseline.

6.2.3 Adjustments for Covariates

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.

For continuous outcome variables, baseline values of the dependent variable and NYHA functional class (as a binary stratification variable) will be included in the statistical model .

6.2.4 Multiple Comparisons/Multiplicity

No adjustments for multiplicity will be made.

6.2.5 Subgroups

No subgroups analyses are planned.

6.2.6 Missing, Unused, and Spurious Data

The handling of intercurrent events (ICEs) and sensitivity analyses are described in Section 6.4. No other imputation of missing efficacy endpoints will be used.

In all listings, missing or incomplete dates in safety data will be left as they have been recorded. However, for calculation and sorting based on dates and for consideration in summary tables, the following method will be used:

For partial or missing adverse event (AE) start dates the following imputation will be applied:

1. If year is not missing and is after the year of first dose:
    a. If month is missing, then month will be imputed as January.
    b. If day is missing, then day will be imputed as the first of the month.

2. If year is not missing and is the same as the year of the first dose:

   a. If month is missing, then impute the month as the month of the first dose date.

   b. If day is missing, and the month is the same as the month of the first dose date, then impute day as the day of the first dose date.

   c. If day is missing but month is after the month of first dose date, then impute day as the first day of the month.

3. If year is missing then impute the year as the year of the first dose date:

   a. If month is missing, then impute the month as the month of the first dose date.

   b. If day is missing, then impute the day as the day of the first dose date.

4. If the start date is completely missing, but the AE is either ongoing or the stop date is after the first dose date then impute the start date as the first dose date.

5. For any cases involving the rules above, if the AE end date is before the AE start date, then do not impute the AE start date and assume that the AE is treatment emergent for the purpose of the analysis. Further, if the AE stop date occurs prior to the first dose date, do not impute the AE start date, and assume that the AE is not treatment emergent.

No imputations will be applied to AE stop dates.

A missing/incomplete date of medical comorbidities or disease diagnosis will be assumed to have occurred before any study treatment.

Missing AE relationship data will be assigned the 'related' category for treatment emergent AE.

6.3 Study Population

6.3.1 Subject Disposition

Subject disposition will be presented, including the number screened, the number dosed, the number that withdrew from study treatment and from the study along with the reasons. The number of subjects in each analysis set will also be presented.

The summaries will be presented by treatment group and overall. The denominator for all percentages will be the total number of subjects in each treatment group.

The following by-subject listings will be presented.

- Study completion information, including the reason for premature study withdrawal.
- Inclusion/exclusion criteria

- Inclusion in study analysis sets
- Protocol deviations
- Reasons for exclusion from the per protocol sets

6.3.2 Demographic and Baseline Characteristics

Treatment groups will be described for the FAS 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, NYHA functional class). The preference will be to present these baseline results without formal statistical testing; however, journal preference, editorial preference, and reviewer preference on this issue vary widely despite published CONSORT guidance. On request, 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. The analyses may be repeated for other subject subsets (e.g., PPS1, PPS2) if some risks of imbalance are revealed during the data analysis.

Medical comorbidities will be coded using MeDRA dictionary (see Section 5.1) and summarized by System Organ Class (SOC) and Preferred Term (PT). No formal statistical comparisons will be performed.

Demographic and baseline data will be provided in data listings.

6.3.3 Prior Medication

Prior and concomitant medications will be coded using the WHO Drug dictionary (see Section 5.1).

Prior medications will be defined as any medication with a start date before the date of first dose of study medication.

Medications with a start date on or after the date of first dose of study medication and not after the last dose of study medication will be considered concomitant. Medications taken prior to the first dose of study medication and continuing after the first dose of study medication will be considered both prior and concomitant.

If a medication date or time is missing, or partially missing, and it cannot be determined whether it was taken on or after start of treatment, it will be considered both prior and concomitant medication.

Results will be tabulated by Anatomic Therapeutic Class (ATC) and preferred term.

The use of prior and concomitant medications will be included in by-subject data listing.

6.3.4 Exposure and Compliance

Summary statistics of the duration of exposure, number of doses and the percent compliance will be presented. Percentage compliance will also be summarized by category (<=60%, >60%-80%, >80-100%, >100%-120%, >120%, and >=80%). The number and percentage of participants who reported taking the study drug as directed and the primary reasons for not taking the study drug as directed will be summarized by visit.

Duration of exposure (days) will be defined as Last Dose Date – Start Dose Date + 1.

Percentage compliance will be defined as Number of doses taken/ Number of doses expected *100.

Number of doses taken will be defined as the number of tablets dispensed – number of tablets returned.

Number of doses expected will be defined as duration of exposure (days)*planned daily dose.

6.4 Efficacy Evaluation

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.

6.4.1 Primary efficacy analysis

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 for the FAS 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 distance, 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.

PAH etiology in the analysis will be as follows:

- Idiopathic
- Familial
- Congenital Heart Disease
- Collagen Vascular Disease
- Toxin
- Portopulmonary Hypertension

6.4.1.1 Sensitivity analysis

Sensitivity analyses will be performed using the PPS1 and PPS2 analysis sets instead of FAS.

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.

Sensitivity analyses of the primary endpoint will include:

1) • a linear regression model using a worst case scenario (WCS) method of imputation

2) • 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 functional class using least squares and robust standard error estimates.

For all methods, treatment effect estimates and 95% CIs will be presented.

6.4.1.2 Additional analyses

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 NYHA functional class (stratification variable) will be used. The odds ratio 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.

6.4.2 Secondary analysis

Secondary endpoints include the change in BNP, NYHA functional class, right ventricular basal diameter, TAPSE, emPHasis-10 score, and the number of participants with an escalation of routine clinical treatments for PAH during the trial.

The main analysis for each secondary endpoint will be performed for the FAS. Sensitivity analyses will be performed using the PPS1 and PPS2 analysis sets instead of FAS. Sensitivity analyses using worst case scenario and complete case analysis will be performed for the FAS.

6.4.2.1 BNP

Summary statistics (mean, standard deviation, median and range) of BNP (untransformed and log-transformed) and change from baseline for each visit will be presented by treatment group. Change in log-transformed value 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 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 for BNP will be set to the highest value in the observed population.

6.4.2.2 NYHA functional class

Summary tabulations of the number and percentage of participants within each NYHA functional class for each visit will be presented by treatment group. NYHA functional class will be evaluated between the treatment groups using ordinal logistic regression adjusted for the baseline NYHA functional class (stratification variable). The odds ratio with 95% CIs will be reported.

Missing data 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) but for categorical variables [3]. The worst case scenario for NYHA functional class will be assumed to be IV.

6.4.2.3 Right ventricular basal diameter

Summary statistics (mean, standard deviation, median and range) of right ventricular basal diameter and change from baseline for each visit will be presented by treatment group. Change from baseline 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.

Missing data 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 for right ventricular basal diameter will be set to the highest value in the observed population.

6.4.2.4 TAPSE

Summary statistics (mean, standard deviation, median and range) of TAPSE and change from baseline for each visit will be presented by treatment group. Change from baseline 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.

Missing data 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 for TAPSE will be assumed to be zero.

6.4.2.5 EmPHasis-10 score

Summary statistics (mean, standard deviation, median and range) of emPHasis-10 score and change from baseline for each visit will be presented by treatment group. Change from baseline 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.

Missing data 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 for emPHasis-10 score will be assumed to be 50.

6.4.2.6 Escalation of routine clinical treatments for PAH

Summary tabulations of the number and percentage of participants with an escalation of routine clinical treatments for PAH for each visit will be presented by treatment group.

Escalation of routine clinical treatments for PAH will be analyzed as a categorical variable (yes / no escalation). A Cochran-Mantel-Haenszel (CMH) test with adjustment for the stratification factor baseline NYHA functional class will be used to test the null hypothesis of no treatment effect during the trial for famotidine vs. placebo with regards to the proportion of subjects with an escalation of routine clinical treatments for PAH.

Odds ratios will be estimated from the CMH test together with the associated 95% confidence intervals (CIs) and corresponding p-values. The proportion per treatment arm will be displayed together with exact Clopper-Pearson 95% CIs. In addition, the common risk difference between famotidine and placebo will be provided, along with 95% confidence interval (stratified Newcombe confidence limits).

Missing data 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) but for categorical variables [3]. The worst case scenario for a participant will be assumed to have escalated PAH specific care.

6.4.3 Sub-study analysis

There are two sub-studies proposed for this trial. One sub-study involves cardiopulmonary exercise testing and the other sub-study involves invasive hemodynamic evaluation using right heart catheterization.

6.4.3.1 Cardiopulmonary exercise testing (CPET) sub-study

Summary statistics (mean, standard deviation, median and range) of CPET sub-study results and change from baseline for each visit will be presented by treatment group. The following metrics of the exercise response will be summarized:

- Peak VO2 (mL/min)
- Peak Weight adjusted VO2 (mL/kg/min)
- Ve/VCO2 slope
- Achieved watts (watt)

6.4.3.2 Right heart catheterization (RHC) sub-study

Summary statistics (mean, standard deviation, median and range) of RHC sub-study results and change from baseline for each visit will be presented by treatment group. The following results will be summarized:

- Thermodilution stroke volume Index (mL/m2)
- Right atrial pressure (mmHg)
- Pulmonary Arterial Pressure Systolic (mmHg)
- Pulmonary Arterial Pressure Diastolic (mmHg)
- Mean Pulmonary Arterial Pressure (mmHg)
- Pulmonary capillary wedge pressure (mmHg)
- Thermodilution pulmonary vascular resistance (wood units)

6.4.4 Exploratory analysis

Pre-planned exploratory analysis: Etiology of PAH or sex may lead to effect modification in the relationship between study drug and outcomes. A subgroup analysis will be repeated for any group with at least 10 participants (e.g., men, women, toxin-induced PAH, idiopathic PAH, etc). The primary purpose of these analyses will be to inform subsequent trial design; however, if these individual analyses are reported it will be with the tempered inference informed by the fact that these sub-groups may not be balanced between active drug and placebo, are meant to be hypothesis generating only, and are underpowered as shown in the following table depicting the power to detect a minimally important difference in six-minute walk distance (assuming balanced groups which may not be true).

Alpha	Group size	Power
0.05	10	0.22
0.05	12	0.27
0.05	14	0.31
0.05	16	0.35
0.05	20	0.39

6.5 Pharmacokinetic Evaluations

Not applicable.

6.6 Safety Evaluations

Safety analyses will be conducted using the Safety Analysis Set.

6.6.1 Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), see Section 5.1, and displayed in tables and listings using System/Organ/Class (SOC) and Preferred Term (PT).

Analyses of adverse events will be performed for those events that are considered treatment emergent, where treatment emergent is defined as any adverse event with onset after the administration of study medication through the end of the study (see Section 5.2) or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the investigator through the end of the study.

Adverse events are summarized by subject, therefore, in any tabulation, a subject contributes only once to the count for a given adverse event (SOC or preferred term).

The number and percentage of subjects with any treatment-emergent adverse event (TEAE), any treatment-emergent adverse event by severity, with any treatment-emergent adverse event by relationship to study drug, with any treatment-emergent adverse event leading to withdrawal from study drug, and with any treatment-emergent serious adverse event (SAE) will be summarized by treatment group and overall. In these tabulations, each subject will contribute only once (i.e., the most related occurrence or the most intense occurrence), regardless of the number of episodes. The number of events and the average number of events will also be provided in tabulations of TEAEs and serious TEAEs.

Adverse events with definite, probable, and possible relationship are considered related to study drug. Adverse events with unrelated and unlikely relationship are considered unrelated to study drug.

Histograms showing the frequency of the number of treatment-emergent AEs and SAEs in each treatment group will be included.

Exposure-adjusted event rates by treatment group and overall will be provided for participants with TEAEs, and with serious TEAEs. Each summary will present by decreasing incidence of PT per 100 subject years of exposure, calculated as (number of subjects with event/total patient-years). Years of exposure is either a) time from first treatment until start date of TEAE type or b) duration of exposure for subjects without a TEAE type. 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.

The number and percentage of subjects with TEAE with hospitalization required will be summarized by treatment group and overall, including the number of events, the average number of events and the exposure-adjusted event rates. Poisson regression modeling will be used to derive rate ratios and 95% CIs to compare hospitalization rates between treatment groups.

All adverse events occurring on study will be listed in subject data listings.

By-subject listings also will be provided for the following: subject deaths; serious adverse events; adverse events leading to withdrawal and adverse events with hospitalization required.

6.6.2 Laboratory Data

Safety laboratory data at each study visit and changes from baseline will be summarized by treatment group. Laboratory parameters will be reported in original units without conversion, see Table 9-2.

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).

All laboratory data will be provided in data listings.

A subset listing will be presented for all abnormal laboratory values.

6.6.3 Vital Signs and Physical Examinations

The actual value and change from baseline to each on study evaluation will be summarized for vital signs.

By-subject listings of vital sign measurements will be presented in data listings.

6.6.4 Electrocardiogram

Not applicable.

7 CHANGES TO PLANNED ANALYSES

The following are changes between the protocol-defined statistical analyses and those presented in this statistical analysis plan:

The FAS will be the primary analysis set for the analysis of the primary and secondary efficacy endpoints rather than ITT. FAS includes all randomized subjects who received at least 1 dose of study medication. Subjects will be analyzed according to their randomized treatment.

Safety analysis set will be the primary set for the analysis of the safety parameters and it includes all randomized subjects who received at least 1 dose of study medication. Subjects will be analyzed according to their actual treatment. Actual treatment is defined as the treatment received for most of the days during the treatment phase of the study.

The data of NYHA functional class will be considered to be ordinal categorical values in the analysis. Change from baseline in NYHA functional class will be evaluated between the treatment groups using logistic regression adjusted for the baseline NYHA functional class (stratification variable). Missing data 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) but for categorical variables.

The data of escalation of routine clinical treatments for PAH will be analyzed as a binary categorical variable (yes / no escalation). A Cochran-Mantel-Haenszel (CMH) test with adjustment for the stratification factor baseline NYHA functional class will be used to test the null hypothesis of no treatment effect during the trial for famotidine vs. placebo with regards to the proportion of subjects with an escalation of routine clinical treatments for PAH. Missing data 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) but for categorical variables.

8 REFERENCES

1. International Council on Harmonization, Statistical Principles for Clinical Trials (ICH E9)

2. International Council on Harmonization, Statistical Principles for Clinical Trials Addendum (ICH E9 R1)

3. Imputation of Categorical Variables with PROC MI. Paul D. Allison, University of Pennsylvania, Philadelphia, PA.

9 APPENDICES

9.1 Schedule of Assessments

Table 9-1: Schedule of assessments

	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
Miscellaneous							
Data Safety Monitoring Board		Semi-annually					

As per clinical practice guidelines, patients will be seen every three 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. 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 H2 antagonists, the emPHasis-10 score, study procedures, and sub-study components.

9.2 Estimands

Not applicable.

9.3 Laboratory Conversion Factors

Laboratory parameters will be reported in original units without conversion, see Table 9-2.

Table 9-2: Laboratory parameters

Parameter (unit)
Sodium (mEq/L)
Potassium (mEq/L)
BUN (mEq/L)
Creatinine (mEq/L)
WBC (thou/uL)
Hemoglobin (g/dL)
Platelets (thou/uL)
BNP (pg/mL)
Calcium (mg/dL)

10 LIST OF STATISTICAL OUTPUTS

The list of statistical outputs is provided in a separate file. This avoids duplication since it will be part of the mock shells.

UW REHAB-PH Statistical Analysis Plan Final Version 1.00 2023-08-30

Final Audit Report 2023-08-30

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