Supplementary Material

Methods:

Study Design

This was an investigator initiated, randomized (1:1), placebo controlled phase Ib study of acute administration with hemodynamic monitoring of a single dose of study drug (ranolazine or placebo), followed by 12-weeks of daily administration. All patients seen at the University of Chicago (UC) PH clinic that met the inclusion criteria had the opportunity to enroll in the study.

This study was conducted at the UC. Gilead, Inc. (manufacturer of ranolazine) permitted use of the drug and supported the conduct of the study at the UC by its investigator-initiated study mechanisms. The Food and Drug Administration exempted the study from an Investigational New Drug requirement. The UC Institutional Review Board approved the consent and the protocol. The risk/benefit was justified based on the poor long-term prognosis of the enrolled patient population, the routine safety surveillance conducted jointly by experts in PAH and the use of ranolazine in chronic stable angina patients and close surveillance of outpatients familiar with individualized titration of other PAH therapeutics. The procedures were in accordance with the ethical standards of the Helsinki Declaration. All subjects provided written informed consent.

Patients

Inclusion Criteria

PAH patients ages 18-72 years, defined as idiopathic PAH, heritable PAH or PAH associated with connective tissue disease, congenital heart disease (repaired), or drug/toxin use [8], World Health Organization (WHO) Functional Class (FC) I-III, with a historic diagnostic right heart catheterization of PAH as defined as: mean pulmonary

artery pressure (PAP) ≥25 millimeters of mercury (mmHg) with a normal wedge pressure (PCWP) ≤ 15 mm Hg at rest and a pulmonary vascular resistance (PVR) >3 Wood units were enrolled (11/2011 to 9/2013). Baseline six-minute walk test (6MW) ≥150 meters (without an upper limit) [9]. All patients had a cardiopulmonary stress test (CPET)[10-14], 2-dimenstional (2D) and 3-dimensional echocardiography (3DE) [15,16], and administration of the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) quality of life questionnaire [17,18] performed ≤ 21 days prior to enrollment.

Background Therapies

Patients were receiving approved PAH monotherapy or a combination of PAH medications: including, ambrisentan (5,10 milligrams (mg), sildenafil (60-240mg), tadalafil (40mg), epoprostenol, treprostinil, or iloprost at stable doses for >90days. Patients could also be receiving conventional PAH therapy as clinically indicated (oxygen, calcium channel blockers, digoxin) provided the dose was not changed in the 30 days prior to enrollment. Dosing of anticoagulants (warfarin) was considered stable if it was not changed in the 30 days prior to enrollment, except, as needed several days before and after cardiac catheterization.

Exclusion Criteria

Patients were excluded if they were calcium channel blocker responders on monotherapy calcium blockers [8,19] or receiving CY3P4 inducer (i.e. bosentan). Patients with impaired lung function as assessed by a total lung capacity < 60% of predicted or significant obstructive lung disease with forced expiratory volume-1/ forced vital capacity ratio < 70% of predicted were excluded. Patients with systemic hypotension defined as systolic arterial pressure < 90 mmHg or systemic hypertension defined as systolic arterial pressure ≥140 mmHg and a diastolic arterial pressure ≥ 90 mmHg despite

adequate medical therapy were excluded. Patients with impaired liver function tests (aspartate aminotransferase, alanine aminotransferase, total bilirubin, and alkaline phosphatase) >2X normal values and/or renal insufficiency defined as creatinine clearance <30 ml/min as defined by the Cockcroft-Gault formula: Male: Creatinine clearance (ml/min)= (140-age) x (body weight in kg)/ (72 x serum creatinine in mg/dl); Female: Creatinine clearance (ml/min)= 0.85 (140-age) x (body weight in kg)/ (72 x serum creatinine in mg/dl) were excluded.

Echocardiography Image Acquistion:

2D Echocardiography

Comprehensive 2D and color Doppler evaluation was performed by an experienced sonographer using an iE33 imaging system equipped with an S5 transducer (Philips Healthcare, Andover, MA) with digital loops stored and analyzed offline (Xcelera Workstation, Philips). Right and left heart measurements were made according to published guidelines.[20] Using vendor-independent software (Epsilon Imaging) peak systolic free wall longitudinal strain of the RV was also measured.

Left ventricular ejection fraction (EF) was calculated using the biplane Simpson's method. Left atrial volume measurements were made using the area-length method.[21] RV basal (maximal dimension in the lower third) and mid- (maximal dimension in the middle third) cavity measurements were made in the RV-focused apical 4-chamber view in end-diastole (ED). RV wall thickness was estimated at end-diastole on a 2D frame in the subcostal view at the level of the tricuspid valve chordae[22]. Fractional area change (FAC), defined as ((ED) area – end-systolic (ES) area)/ED area x100 was also measured using the RV-focussed apical 4-chamber view. ED and ES were defined as the frames depicting the largest and smallest RV cavity size, respectively. Tricuspid

annular plane systolic excursion (TAPSE) was obtained via M-mode through the lateral wall of the tricuspid annulus. The velocity of the tricuspid anular systolic motion (RV S') was measured by placing the pulsed tissue Doppler sample volume at the lateral wall of the tricuspid annulus in the apical 4-chamber view and recording the maximal systolic excursion velocity from the resulting signal. Peak tricuspid regurgitation (TR) gradient (in mmHg) was measured using the modified Bernoulli equation, from the maximal TR jet velocity. Systolic PAP was estimated using the TR gradient and adding an approximation of RA pressure based on inferior vena cava size and collapsibility.[22]

2D longitudinal speckle-tracking analysis of the RV free wall was performed in the RV-focussed apical 4-chamber view, using vendor-independent, commercially available software (Epsilon Imaging). After manual verification of end-diastolic and systolic frames, the endocardial border of the RV free wall was manually traced and automatically tracked throughout the cardiac cycle. Peak systolic longitudinal strain of the RV free wall (RV FWLS) was calculated at end-systole. RV FWLS is defined as the percentage of myocardial shortening relative to the original length and is conventionally presented as a negative value. Therefore, the more negative the value, the more preserved is the shortening.

3D echocardiography

3DE images of the RV were acquired from a modified apical 4-chamber view (Philips iE33 Healthcare, Andover, MA) with a fully sampled matrix-array transducer (model X7-2t). Full-volume acquisition was performed using ECG-gating over 4 consecutive cardiac cycles during a breath-hold. Digitally saved 3DE datasets were analyzed (4D RV-Function 1.1, TomTec Imaging Systems, Unterschleissheim, Germany) to quantify RV ED and ES volumes as well as RV ejection fraction. This required manual initialization of

contours in user-defined end-systolic and ED frames in the apical 4-chamber, coronal, and sagittal views, while including the trabeculae in the RV cavity. [15]

Cardiopulmonary Exercise Testing (CPET)

The test was administered by one of two trained exercise physiologists in the stress test area across the hall from the pulmonary hypertension clinic. The data were analyzed by one of two advanced heart failure cardiologists who were blinded to treatment assignment. Following an explanation of the exercise study and related procedures, each patient performed a physician-supervised, symptom-limited, progressively increasing exercise test on a treadmill. The test was un-encouraged. We monitored heart rate, blood pressure, electrocardiography, and gas exchange, breath-by-breath. All patients were off oxygen therapy in order to perform the test.

The protocol consisted of 5 min of rest, followed by interval walking at first 4 minutes followed by increases in speed/elevation at 2-minute intervals until maximum tolerance; additional data was collected up to 5 minutes into recovery. Recordings were made during the last 15 seconds of each interval with gas exchange measurements. During these intervals, the speed and grade (incline) were increased (Naughton-Balke, see appendix). Gas exchange measurements were computer-calculated breath-by breath and averaged over 15 second intervals using a diagnostic system (Cardiorespiratory Diagnostic System; Medical Graphics, MN). [23] The volumes of the flowmeter and mouthpiece (50ml x breathing frequency) were subtracted from minute ventilation (VE) for the VE/VCO_2 calculations. [23] Anaerobic threshold was determined by the V-slope method. [23] Metabolic equivalents (METs) were estimated and reported using standardized formulas.

Six-minute walk (6MW) testing

The standardized 6MW exercise test was administered by one of three trained technicians in accordance with American Thoracic Society guidelines. The test was administered in a 100-foot hallway within the clinic, with 10-foot demarcations starting at zero. [9]

Acute hemodynamic testing

Right heart catheterization:

Each patient underwent a right heart catheterization by standard technique. [24] An 8 French sheath was placed in the right internal jugular vein via a modified Seldinger technique. Prior to obtaining invasive hemodynamic measurements, 10cc of blood was collected for storage for future biomarker analysis and 7cc blood was collected for pre-drug or post-drug plasma levels. A 7.5 French balloon directed thermodilution PA catheter was placed in the venous circulation and passed into the pulmonary artery. Pressures were recorded, cardiac outputs measured with the thermodilution technique, and blood was drawn for measurements of oxygen saturations. Oximetry and the electrocardiography tracing were monitored continuously and systemic blood pressure was monitored using a noninvasive cuff every 10 min. Patients received oxygen (O_2) supplementation to maintain an O_2 saturation ≥ 92%. Baseline measurements included mean right atrial (mRA) pressure, systolic, diastolic and mean PAP, PAWP (measured at end-expiration), cardiac output/cardiac index (CO/CI) by thermodilution, in triplicate, and PA O_2 saturation. PVR was calculated using the standard formula and expressed in Wood units. After baseline measurements, the catheter was left in place to allow for subsequent measurements after administration of active study drug or placebo.

Acute Study Treatment:

Patients were given either placebo or ranolazine sustained release at a dose of 500mg. Hemodynamic measurements were repeated at 0, 60, 90, 120, 240, and 360 minutes (min). Patients were monitored in a telemetry bed during this time. Plasma levels of ranolazine were drawn at each of the above time points via the PA catheter. Hemodynamics measurements were taken within 5 min of the scheduled time. Heart rate and systemic blood pressures were recorded at these times and throughout the observation period. After the acute monitoring phase, patients were discharged home.

Pharmacokinetic (PK) analysis:

Plasma samples for PK studies of ranolazine were drawn during hemodynamic measurements at 0, 60, 90, 120, 240, and 360 min from the patient's Swan-Ganz catheter into a syringe and aliquoted by a 20 gauge or larger bore needled into one 10 ml lavender-top (ethylenediaminetetraacetic acid, EDTA) tube. The tubes was inverted three times and placed on ice. Within 30 minutes of collection, plasma was separated by centrifugation at 1300 grams for 15 minutes at 4^{o}C. The separated plasma was transferred in aliquots to polypropylene cryovials and stored at -70^{o}C. Analyses were performed by Intertek Pharmaceutical Services.

Follow-up and Treatment

After discharge, patients received a phone call at 24 and 48 hours to assess their clinical status, which included an assessment of adverse events and FC. Patients returned to the clinic at weeks 4, and 8 for assessment of clinical status, repeat laboratory testing, CAMPHOR questionnaire, and adverse events. At week 4, patients were up titrated from 500 mg to 1000mg daily. At week 12, all objective measures were repeated: FC, laboratory testing, 2D and 3DE, CPET, 6MW, cardiac catheterization hemodynamics,

and CAMPHOR questionnaire. A blood sample was drawn for PK analysis from a peripheral vein through a 21 or larger gauge needle into a 10 ml lavender top (EDTA) tube.

Withdrawal Criteria/Data Safety Monitoring Board

All patients with serious adverse events were discussed with the Data Safety Monitoring Board (DSMB) prior to withdrawal. The DSMB consisted of 2 outside PAH experts (RS and RO) with experience in trial design and the acute care of PAH patients. The DSMB received reports of all serious adverse events and updates after each enrollment with formal updates after 3 patients completed 12 weeks and then monthly as per the DSMB charter.

Extension Phase

Patients had the option of continuing on study drug at the discretion of the physician. The patient and the study team remained blinded until the completion of the 12-week phase by the final patient. All patients received 500mg in the extension phase and up-titrated to 1000mg at their week 4 visit. At the 12 week visit in open label, patients had a blood sample was drawn from a peripheral vein through a 21 or larger gauge needle into a 10 ml lavender top (EDTA) tube for PK analysis. Based on objective clinical improvement, at the end of the study duration, patients had the option to continue receiving study drug at the discretion of the investigator for up to 1 year (or until all patients are un-blinded from the study, whichever came last). After this time, patients were un-blinded and if on ranolazine, could continue on commercial therapy. If the patient's health insurance did not cover the cost of commercial medication, the study sponsor could help patients obtain the drug at a reduced or no cost. Visits were standard of care 3-6 month visits with procedures as determined by the investigator.

Enrolled open-label patients continued to be followed as standard of care.

Sample Size and Statistical Analysis

This was a pilot study planned to assess the acute and 12-week response to treatment and safety in 20 patients. The placebo group was the comparator group. Allowing for 10% drop out rate, a total of 22 patients was planned to determine adequate safety exposure. However based on site enrollment feasibility, the principal investigator and DSMB chose to stop finish enrollment after 12 patients completed 12-weeks of therapy. All categorical variables are described in median +/- interquartile range. Comparisons between groups were made using Fisher exact test or the Mann-Whitney test.

DSMB Charter- A Phase 1 study of ranolazine acute administration and short term administration in pulmonary arterial hypertension

Introduction

The Data Safety Monitoring Board (DSMB) is the safety review board for the phase 1 study of acute and short term ranolazine administration in pulmonary arterial hypertension (PAH). The DSMB will periodically review the safety results, evaluate the treatment for excess adverse events, determine whether the basic trial assumptions remain valid, judge whether the overall integrity and conduct of the trial remain acceptable, and make recommendations to the Primary Investigator (PI) and study team.

Organization

Data and safety monitorin*g* will be conducted by the PI and the local IRB. Additionally, 2 outside PAH experts with experience in trial design and the acute care of PAH patients will be chosen to oversee the study and act as a DSMB.

The DSMB will teleconference as needed with the PI after receiving a formal bimonthly update from Ms. Glassner via email.

The DSMB consists of 2 outside PAH experts:

- Ronald J. Oudiz, MD, FACP, FACC, FCCP (Cardiology)
- Robert Schilz, DO, PhD (Pulmonology)

The DSMB members together form a group with expertise in:

- relevant clinical practice
- clinical trial methodology

Responsibilities and Functions

The DSMB members will review and approve the DSMB charter. After this approval, and at periodic intervals throughout the course of the trial, the DSMB responsibilities are to:

- Protect the safety of the study participants;
- Evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, participant risk versus benefit, performance of the trial site, and other factors that can affect study outcome;
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- Report on the safety and progress of the trial;
- Make recommendations to the PI, and if required, to the Food and Drug Administration (FDA) and Institutional Review Board (IRB) concerning continuation, termination or other modifications of the trial based on the observed side effects of the treatment under study;
- Ensure the confidentiality of the trial data and the results of monitoring;

- Assist the PI/Sponsor by commenting on any problems with study conduct and/or data collection.

The DSMB primary role is to assure the safety of the patients and to assure the investigators and the medical community that the risks of this trial are being evaluated and the patients' safety is being kept foremost in mind.

Reports to DSMB

All data presented to the DSMB and subsequent deliberations are strictly confidential. The DSMB is privy to statistical data and serious adverse event reports required for its deliberations. The DSMB reviews interim reports of patient accrual and exploratory outcome measures provided by the study site. Interim reports typically include tabulations of study patient characteristics, major clinical events, and exploratory outcomes. <u>These reports will occur formally after 3 patients complete 12 weeks, after 10 patients, and at the conclusion of 20 patients.</u> If outcome data have accrued, the study site presents a formal interim analysis of the primary outcome and hypothesis testing. After reviewing each such report, the DSMB assesses the need to perform further in-depth evaluation of the benefits and risks of the study.

Monitoring and Reporting Adverse Events

Adverse events (AE's) will be recorded on the appropriate Adverse Event Form for the study in which the patient was enrolled. AE's will be classified according to the relationship between the study intervention and the AE ("unrelated," "unlikely related," "possibly related," "probably related," and "related") and the severity of the AE ("not serious" and "serious.") **Reports of all serious adverse events will be submitted by the study site to the local IRB within one working day of the event. The study site will report the serious adverse event to the DSMB as soon as possible and no later than seven calendar days after the event.**

- Expedited reporting is required for serious adverse events that are unexpected
- If the unexpected events are life-threatening or fatal, they are to be reported within 7 calendar days
- All other serious and unexpected events should be reported within 15 calendar days

Definitions

1. Serious adverse events include those which are fatal or life threatening; result in significant or persistent disability; require prolonged hospitalization; result in significant intervention such as major surgery; or in the opinion of the investigators, represent other significant hazards or potentially serious harm to research subjects or others.
2. Unexpected events are those which have not been described in the package insert for a given drug/intervention, in the protocol, or in the informed consent document.

APPENDIX I – Study Objectives, Endpoints, and Hypotheses

Primary objective

- To estimate the effect of ranolazine administration on acute hemodynamics
- To assess safety of ranolazine acutely and after 3 months of therapy
- To assess changes in right ventricular function after 3 months of therapy

Primary endpoint

- Change in pulmonary vascular resistance (PVR) acutely

Secondary endpoints

- Change in CPET (VE/VCO2, PETCO2, peak VO2, peak HR, peak RER, work max (MET or Watt), sub maximum exercise time at 3 months
- Change in RV echo parameters 2D and 3D at 3 months
- Change in 6MWD at 3 months
- Safety as assessed by adverse and serious adverse events

Hypotheses

- Ranolazine will lower mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR)
- Ranolazine will have no significant effect on systemic blood pressure
- Ranolazine will be well tolerated with no significant side effects during the time of the study

APPENDIX II – Adverse Events

In prior studies of ranolazine, the AE's that were most frequently attributed to the study compound were constipation, dizziness, and nausea. These AE's were determined to be dose dependent. See the Ranolazine Investigator's Brochure for additional information. Specifically, see Appendix A for a list of expected events.

The informed consent form for this study lists the common side effects of ranolazine as follows:

- constipation,
- dizziness,
- nausea,
- headace,
- diarrhea,
- and abdominal upset.

TITLE: A Phase I study of ranolazine acute administration and short term administration in pulmonary hypertension

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1. Objectives

1.1 Study Design:

This is an randomized placebo controlled single center phase I pilot study to assess the acute vasoreactivity of ranolazine and the safety and potential efficacy of ranolazine in pulmonary arterial hypertension (PAH) patients. A total of 20 patients will be randomized10 to placebo and 10 to active therapy.

1.2 Primary objective:

-To estimate the effect of ranolazine administration on acute hemodynamics.
-To assess safety of ranolazine acutely and after 3 months of therapy
-To assess changes in right ventricular function after 3 months of therapy.

1.3 Primary endpoint: Change in pulmonary vascular resistance (PVR) acutely

1.4 Secondary endpoints:

- Change in CPET (VE/VCO2, PETCO2, peak VO2, peak HR, peak RER, work max (MET or Watt), sub maximum exercise time at 3 months
- Change in RV echo parameters 2D and 3D at 3 months
- Change in 6MWD at 3 months
- Safety as assessed by adverse and serious adverse events.

1.5 Hypotheses:

1) Ranolazine will lower mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR)
2) Ranolazine will have no significant effect on systemic blood pressure Ranolazine will be well tolerated with no significant side effects during the time of the study.

Pharmacokinetics

The immediate release ranolazine (not in current use)had an average terminal elimination half life ranging from 1.4 to 1.9 hours with a dosing of 240 to 400 mg three times per day.6 Sustained release ranolazine has a prolonged absorption phase with maximal plasma concentration (C max) typically seen 4 to 6 hours after administration. The average terminal elimination half-life is ≈7 hours after multiple dosing to steady state and the peak trough difference is 1.6 fold with dosing of 500 to 1000mg twice daily. Steady state is generally achieved within 3 days of twice daily dosing. Ranolazine plasma concentrations that are therapeutically effective for chronic angina is in the range of 2 to 6 μmol/L. Absorption of ranolazine is not affected by food. Oral bioavailability is in the range of 30-50%. Plasma protein binding (mainly to α1-acid glycoprotein) is >65%. The cytochromeP450 (CYP) 3A4- mediated pathway accounts for the

majority of ranolazine biotransformation. Clearance of ranolazine is reduced by renal insufficiency and moderate hepatic impairment.

Study Protocol

Rationale for enrollment:

It is unethical to perform placebo controlled trials in PAH [1] leading to a focus on combination therapies. [2] Hemodynamic parameters are a central part of diagnosis and management as they are the gold standard for measuring pressure. [3] Drug development trials in PAH focus on acute vasoreactivity of the drug during the catheterization.[4-6] Although trials are ongoing to prove efficacy of many combinations, the hemodynamic effects exist. A recent multi-center trial demonstrated a 15% reduction in PVR in patients on background bosentan with sildenafil as the testing agent.[7] Our group demonstrated in 14 PAH patients on infusion prostacyclin a median decrease of 33% in PVR (IQR 18-54%) with follow-up vasodilatory testing. [8] Future studies will be with combination therapy. A novel therapy, unable to demonstrate an improvement in hemodynamics, will not be clinically successful. Ranolazine is not a direct vasodilator, either central or peripheral; however, we do not know whether it will produce acute and/or chronic reductions in pulmonary pressure in patients with pulmonary vascular disease. There is anecdotal evidence that some subjects with PAH have improved after receiving ranolazine and based on the pharmacology one might expect improvements in right ventricular function and cardiac output in these patients with hypertrophied right ventricles.

Eligibility criteria:

All patients must meet all of the following Inclusion Criteria and none of the Exclusion to be considered for entry/enrollment in the study.
Patients will be enrolled who have planned standard of care cardiac catheterization.

Inclusion criteria:

1. All subjects age 18-72 yrs will have a diagnosis of PAH. PAH as defined as idiopathic PAH, heritable PAH or PAH associated with collagen vascular disease, congenital heart disease (repaired), or anorexigen use.[9] A history of PAH as defined by hemodynamics at diagnosis by right heart catheterization defined as: mean PAP $\geq$25 mmHg with a normal PCWP $\leq$ 15 mm Hg at rest and a PVR >3 Wood units.[9]
2. Baseline 6MW $\geq$150 meters
3. Patients will be receiving FDA approved PAH monotherapy or dual therapy medications: including, ambrisentan (5,10mg), sildenafil (60-240mg), tadalafil (40mg), epoprostenol, treprostinil, or iloprost at stable doses for >90days.
4. Receiving conventional therapy as clinically indicated (oxygen, calcium channel blockers, digoxin) with dose that is unchanged in the preceding 30 days prior to enrollment. This is excluding anticoagulants (warfarin) as the patient's dose may not be stable if the patient is having a cardiac catheterization at baseline within 30 days of enrollment and warfarin is being held.

Exclusion criteria:

1. PAH Category II-IV and Category I associated with all other etiologies: HIV, portopulmonary disease [9]
2. All subjects on monotherapy calcium blockers as "calcium blocker responders" irrespective of therapy
3. All subjects receiving CY3P4 inducer (i.e. bosentan)
4. Subjects with pulmonary hypertension due to significant interstitial lung disease, chronic obstructive pulmonary disease, congestive heart failure, valvular heart disease [9]
5. Subjects with (World Health Organization (WHO) functional Class I or Class IV
6. Subjects with total lung capacity (TLC) < 60% of predicted
7. Subjects with significant obstructive lung disease with FEV1/FVC ratio < 70% of predicted
8. Subjects with hypotension defined as systolic arterial pressure < 90 mmHg at baseline
9. Subjects with hypertension defined as systolic arterial pressure ≥140 mmHg at baseline and a diastolic arterial pressure ≥ 90 mmHg despite adequate medical therapy.
10. Subjects with impaired renal function as defined as creatinine clearance <30 ml/min as defined by the Cockcroft-Gault formula: Male: Creatinine clearance (ml/min)= (140-age) x (body weight in kg)/ (72x serum creatinine in mg/dl); Female: Creatinine clearance (ml/min)= 0.85 (140-age) x (body weight in kg)/ (72x serum creatinine in mg/dl)
11. Subjects with liver function tests (transaminases (AST/ALT), total bilirubin, and alkaline phosphatase) >2X normal values
12. Subjects with acutely decompensated heart failure requiring hospitalization or medication adjustment or hospitalization for any cause within the previous 30 days prior to screening
13. Subjects may not be receiving any other investigational agents
14. Subjects without having taken an serotonin reuptake inhibitor within 3-5 months
13. Subjects with left ventricular ejection fraction ≤45% or left ventricular shortening fracton <0.2
15. Subjects with acute myocardial infarction within 90 days prior to screening
16. Subjects taking nitrates for any medical problem
17. Subjects with a recent (<180 days) history of pulmonary embolism verified by ventilation/perfusion scan, angiogram or spiral CT scan
18. Pregnant or lactating women
19. Subjects with a history of current drug abuse including alcohol
20. History of gastric bypass surgery
21. History of sinus or atrioventricular nodal disease ie. sick sinus syndrome, or second or third degree heart block.

Methods:

Screening/baseline visit:
All subjects after providing informed consent will have a visit verifying that they meet entry criteria. They will have their standard of care clinic visit to assess:

1. Etiology of PAH
2. Documentation of a historic right heart catheterization demonstrating PAH
3. WHO functional class
4. Stability of medications
5. Laboratory testing (hemogram, platelets, liver function testing, basic metabolic profile, and N-terminal basic naturetic protein, a PT/INR, thyroid function, and serum collection for biomarkers),
6. CPET, and if able six minute walk test within 48 hours of screening after CPET
7. Echocardiography: 2-dimensionsal (2D), TAPSE, 3-dimensional (3D)
8. Documentation of a historic pulmonary function test
9. Administration of CAMPHOR questionnaire

Day 1: Acute testing
Right heart catheterization:

- Patients will be NPO prior to the procedure starting at 12AM.
- Female subjects will have a urine pregnancy test
- The patient will have a right heart catherterization by standard technique. An 8 French sheath will be placed in the right internal jugular vein via micropuncture percutaneous technique.
- Prior to obtaining measurements 10cc of blood will be collected for storage for future biomarker analysis.
- A 7.5 French balloon directed thermodilution catheter will be placed in the venous circulation and passed into the pulmonary artery. Pressures will be recorded, cardiac outputs measured with the thermodilution technique, and blood drawn for measurements of oxygen saturations. Oximetry and the ECG tracing will be monitored continuously and systemic blood pressure will be monitored using a noninvasive cuff every 10 min. Patients will receive O2 supplementation to maintain O2 sat ≥ 92%.
- Baseline measurements will include mean right atrial (mRA) pressure, systolic, diastolic and mean pulmonary arterial (PA) pressure, pulmonary artery wedge (PAWP) pressure, cardiac output (CO- by thermodilution in triplicate) and PA O2 saturation. PVR will be calculated using the standard formula and expressed in wood units and as dynes-sec-1-cm-5.

Vasoreactivity testing at baseline:

Once baseline stability is demonstrated (by showing that mean PA pressure and CO differ by ≤ 10% over a 10 min period, pulmonary vasoreactivity will be assessed using adenosine at 50ug/kg/min, up-titrating to a maximum tolerated dose every 2 minutes by 50ug to no more than 200ug/kg/min.

Hemodynamics will be recorded at the maximum tolerated dose of adenosine.

Administration of study drug:

- After re-establishment of baseline measurements (10 minute minimum),
- (i.e. a new set of measurements will be recorded prior to administration of study drug). Subjects will receive either **placebo or ranolazine sustained release at a dose of 500mg**.

- Hemodynamic measurements will be repeated at 60 min, 90 min, 120 min, 240 min, and 360 min. Patients will be monitored in a telemetry bed.

- Plasma levels of ranolazine will be drawn at each time point.

Hemodynamics measurements will be taken within 5 minutes of the scheduled time.

Follow-up 24 and 48 hours:

- Patients will receive a phone call at 24 and 48 hours to assess clinical status. This will be to assess adverse events and functional class

Long Term Follow-up

Month 1:

- Patients will be seen in clinic for history, physical exam, functional class documentation, adverse event reporting, and laboratory testing. Blood will be drawn for serum biomarkers.

- CAMPHOR

- Collect and redistribute drug: **Dose of ranolazine will be up-titrated to 1000mg daily.**

Month 2:

- Patients will be seen in clinic for history, physical exam, functional class documentation, adverse event reporting, and laboratory testing. Blood will be drawn for serum biomarkers.

- CAMPHOR

- Collect and redistribute drug

Month 3:

- Patients will be seen in clinic for history, physical exam, functional class documentation, adverse event reporting, and laboratory testing. Blood will be drawn for serum biomarkers.

- CAMPHOR

- Patients will have 2D and 3D echocardiography

- Patients will perform CPET testing.

- Patients will perform 6MWD ± 2 days

- Right heart catheterization ± 7 days of month 3 visit

Off schedule-evaluations:

Patient's returning for an AE will have an evaluation by the study coordinator and PI and an adverse event documented. Further evaluation for clinical care of the patient will be performed appropriately to the care of the patient and the nature of the AE event. No other evaluations specific to the study will be performed as part of research.

Extension:

Patients will have the option of continuing on study drug at the discretion of the PI. The patient and the PI will remain blinded until the completion of the active phase by the 20th patient. All patients will receive 500mg in extension and up-titrated to 1000mg at month 1. Based on objective clinical improvement, at the end of the study duration, patients will have the option to continue receiving study drug at the discretion of the PI for up to 1 year (or until all patients are unblinded from the study, whichever comes last). After this time, patients will be unblinded and if on ranolazine, it will continue to be available to patients commercially. If the patient's health insurance does not cover the cost of commercial medication, Gilead will help patients obtain the drug at a decreased cost.

Visits will be standard of care 3-6 month visits with standard of care procedures as determined by the PI.

Sample Size and Statistical Analysis:

This is a pilot safety study. We will plan to assess the acute response and 3 month follow-up response in 10 patients. The placebo group will be the comparator group. We will also determine the correlation between changes in PVR after adenosine and in response to ranolazine. Allowing for 10% drop out rate, a total of 22 patients will be required.
Comparisons between groups will be made using Fisher exact test or Chi-square analyses.

Patient Safety: Summary of the Risks and Benefits:

This study involves administration of an agent (ranolazine) with potential benefits in PAH. Thus if patients receive active study drug (ranolazine) rather than placebo, they could potentially experience clinical benefit.

The risks of blood drawing include: bleeding, hematoma, pain, and infection at the insertion site.

The risks of exercise stress testing (6MWD, CPET) include:

Exercise stress tests will be performed by trained professionals in a highly monitored setting. These studies are routinely obtained in clinical practice to access clinical status and are considered safe in this patient cohort. Risks include arrhythmia, pre-syncope, and syncope (all rare events).

The risks of echocardiography include: ecchymosis, mild chest discomfort, claustrophobia, and allergy to the gel. Echocardiography is non-invasive and does not use radiation.

The risks of right heart catheterization include:
Bleeding, hematomas
Infection at the insertion site
Endocarditis (very rare)
Transient cardiac arrhythmias (3%)
Pneumothorax (puncture of the lung, possibly requiring chest tube placement) (1-2%)
Damage to heart valves (very rare)

Pulmonary artery perforation (0.03%)
Pulmonary infarction (<1%)
Minimal radiation exposure- fluroscopy

Ranolazine: Common drug toxicities include: constipation, dizziness, nausea, headache diarrhea, abdominal upset

Informed Consent:

Written informed consent will be obtained from the patient. Confidentiality will be maintained at all times. Consent will be obtained by the principal investigator or one of the co-investigators. Patients will be provided the consent form and the investigator will review the contents of the consent form with the patient/person providing consent and encourage any and all questions. They will be informed that if they decline participation, they will continue to receive all indicated standard care. Patients will be provided a copy of the consent form and a number to contact the investigators with any questions or concerns.

Confidentiality:

Each study participant will be given a PIN number and all data will be entered under that PIN number. There will be a code to convert the reference number into a medical record number, which will be known only by the principal investigator and research staff. The code sheets will be kept in a locked filing cabinet and a password locked computer.

SCHEDULE OF ACTIVITIES: ACUTE PHASE

	Screen	Day 1	24hr f/u call	48 hr f/u call
	≤21 days pre-Day 1			
Informed Consent	X			
Inclusion/exclusion	X			
Medical history	X			
Concomitant medication	X	X	X	X
Adverse events		X	X	X
WHO FC	X	X	X	X
Physical exam	X	X		
Height/Weight	X			
Vital signs	X	X		
Spirometry (FEV_1, FVC and TLC,DLCO)	X			
Pharmacogenomic sample		X		
Laboratory:				
Hematology	X	X		
Chemistry (CMP,amylase, lipase, magnesium, NT-proBNP)	X	X*		
Coagulation (PT, APTT)	X			
Thyroid function	X			
Echocardiogram	X			
CPET	X			
6MW test				
Right heart catheter/adenosine		X		
Dosing at site		X		
Dispense study drug		X		
Blood biomarkers		X		
CAMPHOR	X			

HEMODYNAMICS: Baseline stability mPAP and CO differ by <10% over 10 min
Vasoreactivity= adenosine testing
Repeat at 60min, 90 min, 120 min, 240 min, and 360 min.

* Amylase, lipase, magnesium not needed at day 1.

SCHEDULE OF ACTIVITIES:

	1 month	2 month	3 month
Drug accounting	X	X	X
Concomitant medication	X	X	X
Administer study med/collect pills	X	X	X
Adverse events	X	X	X
WHO FC	X	X	X
Vital signs	X	X	X
Physical exam	X	X	X
CAMPHOR	X	X	X
Laboratory:			
Hematology	X		X
Chemistry **(CMP, NTproBNP)**	X	X	X
Blood biomarkers sample	X	X	X
Echocardiogram			X
CPET			X
6MWT			X
Right heart catheterization			X

Adverse Event Definitions

Adverse Event

Adverse events associated with the use of a drug in humans, whether or not considered drug related, include the following: An adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product. The adverse event does not necessarily have to have a causal relationship with the treatment or usage. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the medicinal product. An adverse event occurs when there is a reasonable possibility that the event occurred purely as a result of the subject's participation in the study (e.g. adverse event or serious adverse event due to discontinuation of anti-hypertensive drugs during wash-out phase) must also be reported as an adverse event even if it is not related to the investigational product.

Examples of adverse events include but are not limited to:

- Abnormal test findings
- Clinically significant symptoms and signs
- Changes in physical examination findings
- Hypersensitivity

Additionally, they may include the signs or symptoms resulting from:
- Drug overdose whether accidental or intentional
- Drug withdrawal
- Drug abuse
- Drug misuse
- Drug interactions
- Drug dependency
- Extravagation
- Exposure in utero

The clinical manifestation of any failure of expected pharmacological action is not recorded as an AE if it is already reflected as a data point captured on the case report form. If, however, the event fulfills any of the criteria for a serious adverse event (SAE), it must be recorded and reported as such.

Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening (immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defect

- Is an important medical event

Life-threatening: The term “life-threatening” in the definition of “serious” refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.

Hospitalization: Any adverse event leading to hospitalization will be considered as Serious, UNLESS at least one of the following exceptions are met:

- The admission is pre-planned (ie, elective or scheduled surgery arranged prior to the start of the study).
  OR
- The admission is not associated with an adverse event (eg, social hospitalization for purposes of respite care).

However it should be noted that invasive treatment during any hospitalization may fulfil the criteria of ‘medically important’ and as such may be reportable as a serious adverse event dependant on clinical judgement. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability means a substantial disruption of a person’s ability to conduct normal life’s functions.

Important medical event: Any adverse event may be considered serious because it may jeopardize the subject and may require intervention to prevent another serious condition. As guidance for determination of important medical events refer to the “WHO Adverse Reaction Terminology – Critical Terms List.” These terms either refer to or might be indicative of a serious disease state. Such reported events warrant special attention because of their possible association with a serious disease state and may lead to more decisive action than reports on other terms.

Unexpected Adverse Event

An unexpected adverse event is any adverse drug event, the specificity or severity of which is not consistent with the current Investigators Brochure (IB) or Package Insert. Also, reports which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected adverse events. For example, an event more specific or more severe than described in the IB or package insert would be considered “unexpected”. Specific examples would be: (1) acute renal failure as a labeled AE with a subsequent new report of interstitial nephritis and (2) hepatitis with a first report of fulminant hepatitis.

“Unexpected,” as used in this definition, refers to an AE that has not been previously observed (eg, included in the IB or package insert), rather than from

the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

Relationship of Adverse Event to Investigational Product

The assessment of the relationship of an adverse event to the administration of study drug is a clinical decision based on all available information at the time of the completion of the case report form.

An assessment of 'No' would include:

1. The existence of a clear alternative explanation, e.g. mechanical bleeding at surgical site.
   OR
2. Non-Plausibility, e.g. the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of 'Yes' indicates that there is a reasonable suspicion that the adverse event is associated with the use of the investigational drug.

Factors to be considered in assessing the relationship of the adverse event to study drug include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- The recovery on discontinuation (de-challenge), recurrence on reintroduction (re-challenge): Subject's response after drug discontinuation (de-challenge) or subjects response after drug re-introduction (re-challenge) should be considered in the view of the usual clinical course of the event in question.
- The underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.
- Known response pattern for this class for drug: Clinical/preclinical
- The pharmacology and pharmacokinetics of the test drug: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the test drug(s), coupled with the individual subject's pharmacodynamics should be considered.

Grading the Intensity (Severity) of the Adverse Event

Adverse events should be graded according to the following general grade definitions:

- Grade 1 (Mild) – Usually transient in nature and generally not interfering with normal activities
- Grade 2 (Moderate) – Sufficiently discomforting to interfere with normal activities
- Grade 3 (Severe) – Prevents normal activities
- Grade 4 – Life-threatening or disabling
- Grade 5 – Death related to the event

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it metone of the criteria for serious adverse events, listed above.

Recording of Adverse Events

All adverse events (serious and non-serious) must be recorded on the CRF from the time the subject has signed the informed consent through 2 days after the dose of study treatment. In addition, the investigator should report any adverse event that may occur after this time period that he/she believes to have a reasonable possibility of being associated with the use of study drug.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. In order to prevent reporting bias, subjects should not be questioned regarding specific occurrence of one or more AEs.

Documentation must be supported by an entry in the subject's file. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome. All AEs must be followed until resolution (ie, complete resolution, stabilization/chronicity, or return to baseline grade).

Per University of Chicago Guidelines, this protocol will be classified as moderate risk. The patients enrolled to this study will be regularly discussed as a part of the weekly Pulmonary Hypertension Research Conference. The discussion at this conference will include patient tolerability and toxicity. A Data and Safety Monitoring worksheet will also be completed at this conference and twenty percent of research charts will be audited annually.

Reporting of Serious Adverse Events

Adverse events including laboratory test abnormalities fulfilling the definition of serious, after signing the informed consent and during follow-up period, must immediately (within 24 hours of the investigator's or research study nurses awareness, or next business day) be reported.

A SAE Report Form must also be completed within 24 hours of the investigator's awareness and forwarded to the IRB. Each SAE must be followed until resolution or stabilization by submission of updated reports.

The University of Chicago study team will report the SAE per the UC IRB reporting policy. The policy is as follows:

Unanticipated problems involving risks to subjects or others refer to a problem, event or information item that is not expected, given the nature of the research procedures and the subject population being studied; and which suggests that the research places subjects or others at a greater risk of harm or discomfort related to the research than was previously known. The IRB considers unanticipated problems, in general, to include any incident, experience, or outcome that meets ALL of the following criteria: unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol, investigator's brochure, drug or device product information, informed consent document, or other research materials; and (b) the characteristics of the subject population being studied, including underlying diseases, behaviors, or traits; related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and suggests that the research places subjects or others at a risk of unknown harm or addition/increased frequency of harms (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

- A completed MedWatch for Mandatory Reporting form (FDA form 3500A) will be prepared by the PI for submission. The University of Chicago team will complete the required paperwork for its IRB. The UC IRB Unanticipated Problem Reporting forms are available on-line at: http://bsdirb.bsd.uchicago.edu/forms-guidelines/documents/unanticipated-problem.pdf . This form must be uploaded on the UC IRB website. Once the forms are completed, the PI will then review, sign and submitted to the UC IRB. This form will also be kept with the nurse coordinator

The University of Chicago study team will notify the FDA of all required expedited safety reports to the FDA within the appropriate regulatory timelines.

- The FDA must be notified of all unexpected fatal or life-threatening events associated with the drug within 7 calendar days of the investigator and/or research study nurse awareness of the event. Events may be phoned, faxed,

or mailed. Each written notification must be submitted on a MedWatch for Mandatory Reporting form (FDA form 3500A) accompanied by a FDA form 1571.

- The FDA must be notified of all adverse events that are both serious and unexpected within 15 calendar days of the investigator and/or research study nurse awareness of the event. Each written notification must be submitted on a MedWatch for Mandatory Reporting form (FDA form 3500A) accompanied by a FDA form 1571.

- A completed MedWatch for Mandatory Reporting form (FDA form 3500A) will be prepared by Onyx Drug safety for submission.

The University of Chicago, when required, will also report all SAEs that require immediate alert (eg, AEs that are serious, unexpected, and related to study drug) to the participating investigators. Upon receiving such notices, the investigator must review and retain the notice with the IB and immediately submit a copy of this information to the local IRB according to local laws and regulations. The investigator and IRB will determine if the ICF requires revision. The investigator must comply with the IRB procedures for reporting other safety information.

Data Collection and Reporting

Biannually there CRFs will be reviewed by U of C personnel. AEs will be tabulated for the entire cohort.

The UC IRB Unanticipated Problem Reporting form is available on-line at http://bsdirb.bsd.uchicago.edu/forms-guidelines/documents/unanticipated-problem.pdf

Records Retention

Records will be kept for at least 5 years. Federal, state, and institutional record retention requirements will be met. Anticipated adverse events include abdominal cramps or upset, nausea and diarrhea. Any deaths will be reported immediately to the IRB.

All Internal and External Unanticipated Problems must be reported to the IRB within 10 working days of investigator's knowledge of the event. (Includes adverse events, protocol deviations, non-compliance, and other events that meet reporting criteria) For Internal Fatal/Life-Threatening Unanticipated Problems, the PI should notify the IRB Chair by phone immediately and consider voluntarily halting subject enrollment.

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3. Badesch DB, Champion HC, Sanchez MA, et al. Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2009;54:S55-66.
4. Grimminger F, Weimann G, Frey R, et al. First acute haemodynamic study of soluble guanylate cyclase stimulator riociguat in pulmonary hypertension. Eur Respir J 2009.
5. Michelakis E, Tymchak W, Lien D, Webster L, Hashimoto K, Archer S. Oral sildenafil is an effective and specific pulmonary vasodilator in patients with pulmonary arterial hypertension. Circulation 2002;105:2398-403.
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9. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54:S43-54.

Appendix: CPET:

The values for peak VO2 in normal persons and the values reflecting below the average are:

Males 20-29 years old: 43±7.2; entry criteria < 28.2 ml/kg/min
Females 20-29 years old: 36±6.9; entry criteria < 21.6 ml/kg/min

Males 30-39 years old: 42±7.0; entry criteria < 25.2 ml/kg/min
Females 30-39 years old: 34±6.2; entry criteria < 20.4 ml/kg/min

Males 40-49 years old: 40±7.2; entry criteria < 24 ml/kg/min
Females 40-49 years old: 32±6.2; entry criteria < 19.2 ml/kg/min

Males 50-59 years old: 36±7.1; entry criteria < 22 ml/kg/min
Females 50-59 years old: 29±5.4 entry criteria < 17.4 ml/kg/min

Males 60-69 years old: 33±7.3; entry criteria <19.8 ml/kg/min
Females 60-69 years old: 27±4.7: entry criteria < 16.2 ml/kg/min

Males _ 70 years old: 29±7.3: entry criteria <17.4 ml/kg/min
Females _ 70 years old: 27±5.8: entry criteria <16.2 ml/kg/min

These values are based on published normal values

WHO Functional Classification of Pulmonary Hypertension

Class I – Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.

Class II – Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.

Class III –Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope.

Class IV – Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any phyical activity.

General Procedures

The 6MW should be administered by the same team throughout the study. The area used for the 6MW should be pre-measured as a minimum of 108 feet (33 meters) in length and at least 6 to 10 feet (2 to 3 meters) in width. The length should be marked with 0.5 meter gradations. The area should be well ventilated with air temperature controlled at 20-23 degrees C (68-76 degrees F). The tester may be at the starting end of the corridor or at the midpoint of the corridor with a stop-watch. Intermittent rest periods are allowed if the patient can no longer continue. I f the patient needs to rest briefly, he/she may stand or sit and then begin again when he/she is sufficiently rested but the clock will continue to run. At the end of 6 minutes, the tester will call "stop" while simultaneously stopping the watch and then measure the distance walked. The Borg Dyspnea Rating will be administered.

0	No breathlessness at all
0.5	Very very slight (just noticeable)
1	Very Slight
2	Slight Breathlessness
3	Moderate
4	Somewhat severe
5	Severe breathlessness
6	
7	Very Severe Breathlessness
8	
9	Very Very Severe

Instructions to the patient: Patients will be instructed that the preceding meal should be light. Patients should be told to wear comfortable clothing and sneakers or comfortable walking shoes. The person administering the test will use the following exact dialogue with the patient:

"The purpose of this test is to find out how far you can walk in 6 minutes. You will start from this point and follow the hallway to the marker (e.g. chair) at the end, turn around and walk back. When you arrive back at the starting point you will go back and forth again. You will go back and forth as many times as you can in the 6 minute period. You may stop and rest if you need to. Just remain where you are until you can go on again. However, the most important thing about the test is that you cover as much ground as you possible can during the 6 minutes. I will tell you the time, and I will let you know when the 6 minutes are up. When I say STOP, please stand right where you are."

I time period for questions will be allotted. The person administering the test will start by saying, "GO" and will tell the patient the time at 2 and 4 minutes by saying, "You have completed 2 minutes, " and then by saying, " You have completed 4 minutes." Eye contact should be avoided with the patient during the test.

Following the walk the Borg scale will be given. “I would like to use the following scale to indicate the maximum shortness of breath you had during the walk test. If there was no shortness of breath at all you would point to 0; if the shortness of breath was not very great you would choose from 0.5 to 2; if you were somewhat more short of breath you would select 3l and if the breathing was getting very difficult, you would choose 4 to 9, dependant on how hard you thought it was; 10 represents the greatest shortness of breath you have ever experienced in your life, and if you feel more short of breath than you have ever been in your life before, choose a number greater than 10. If one of the numbers does not exactly represent how you felt, you can choose a fraction between. For example if you had shortness of breath somewhere between 4 and 5 you could choose 4 ½.”

Right Heart Catheterization Protocol

Right heart catheterization should be performed under fluoroscopic guidance with a triple lumen flow-directed catheter. All procedures will be performed under local anesthesia. All hemodynamic determinations should be made with zero reference level at the mid-axillary line with the patient supine. To ensure reproducibility of this reference level for subsequent measurements and to avoid zero level drift, the transducer should be anchored at the midaxillary line and before each measurement this juxtaposition should be re-achieved. Hemodynamic assessments should be made with the patient in a horizontal position.

Prior to initiation of study drug (if not done within the preceding 14 days) and at week 12, hemodynamic values will be determined by serial measurements of hemodynamic parameters (specifically CO and mPAP) to demonstrate stability. Stable hemodynamics are defined by changes in CO and mPAP of less than or equal to 20% between three consecutive serial measurements at least 5 minutes apart. After hemodynamic stability is demonstrated, the hemodynamics and oxygen saturation variables from the last assessment will be recorded.

CAMPHOR

Cambridge Pulmonary Hypertension Outcome Review

Please read this carefully

On the following pages you will find some statements that have been made by people who have Pulmonary Arterial Hypertension.

Please read each statement carefully.
We would like you to put a check in the box ☒ next to **'Yes'** if you feel it applies to you and a check in the box ☒ next to **'No'** if it does not

Please choose the response that best describes how you feel **today**

Symptoms

Please read each statement carefully and decide if it applies to you ***today***

1. My stamina levels are low	Yes No	❒ ❒
2. I have to rest during the day	Yes No	❒ ❒
3. I feel worn out	Yes No	❒ ❒
4. I get tired very quickly	Yes No	❒ ❒
5. I'm tired all the time	Yes No	❒ ❒
6. I feel very weak	Yes No	❒ ❒
7. I feel completely exhausted	Yes No	❒ ❒
8. I want to sit down all the time	Yes No	❒ ❒
9. I quickly run out of energy	Yes No	❒ ❒

Please turn the page

10. Everything is an effort	Yes ❒ No ❒	
11. I get out of breath when I stand up	Yes ❒ No ❒	
12. I get out of breath when I talk	Yes ❒ No ❒	

Please read each statement carefully and decide if it applies to you ***today***

13. I get out of breath when I walk	Yes ❒ No ❒	
14. I get out of breath when I bend over	Yes ❒ No ❒	
15. I get out of breath when I go up one step	Yes ❒ No ❒	
16. I get out of breath when I walk up a slight incline	Yes ❒ No ❒	
17. I get out of breath without doing anything	Yes ❒ No ❒	
18. I get out of breath climbing a flight of stairs	Yes ❒ No ❒	

19. I have mood swings	Yes ❒ No ❒	
20. I get very down	Yes ❒ No ❒	
21. I rarely feel happy	Yes ❒ No ❒	

Please read each statement carefully and decide if it applies to you ***today***

22. I've forgotten what it's like to enjoy myself	Yes	❒
	No	❒
23. I feel hopeless	Yes	❒
	No	❒
24. My condition gets me down	Yes	❒
	No	❒
25. I often feel anxious	Yes	❒
	No	❒

Please turn the page

Please put a check in the box ☒ under the response which best describes your abilities today**.** For each of the 15 statements please provide one response only.

Please check your response based on your abilities without the use of equipment (for example a cane or walker) or assistance.
Note for daytime oxygen users: Please check your response based on your abilities with your normal oxygen use

Please check <u>only</u> 1 box for each of the following statements	Can do on my own **without** difficulty	Can do on my own **with** difficulty	Cannot do on my own
1. Cut your toenails	ρ	ρ	ρ
2. Bathe yourself	ρ	ρ	ρ
3. Get dressed	ρ	ρ	ρ
4. Walk around inside the house (not including climbing stairs)	ρ	ρ	ρ
5. Walk short distances on level ground	ρ	ρ	ρ
6. Walk longer distances on level ground	ρ	ρ	ρ
7. Walk up a slight incline	ρ	ρ	ρ
8. Climb a flight of stairs	ρ	ρ	ρ
9. Bend down to pick up objects off the floor	ρ	ρ	ρ
10. Stand for a short time	ρ	ρ	ρ
11. Stand for a long time	ρ	ρ	ρ
12. Lift heavy objects	ρ	ρ	ρ
13. Carry heavy objects	ρ	ρ	ρ
14. Do light work around the house or yard	ρ	ρ	ρ
15. Do heavy work around the house or yard	ρ	ρ	ρ

Please turn the page

Quality of Life

Please read each statement carefully and put a check ☒ next to the response that applies best to you ***today***

1. I have to speak softly	True	ρ
	False	ρ
2. I can't be away from home	True	ρ
	False	ρ
3. I've lost interest in food	True	ρ
	False	ρ
4. I don't have the energy for my close relationships	True	ρ
	False	ρ
5. Walking for pleasure is out of the question	True	ρ
	False	ρ
6. My condition puts a strain on my close relationships	True	ρ
	False	ρ
7. I feel very isolated	True	ρ
	False	ρ
8. I can't do things on the spur of the moment	True	ρ
	False	ρ
9. I feel vulnerable when I'm on my own	True	ρ
	False	ρ

10. It feels like my body has let me down	True	ρ
	False	ρ
11. I feel like I'm not in control of my life	True	ρ
	False	ρ
12. I feel dependent on other people	True	ρ
	False	ρ

Please remember to check ***only one*** of the alternative responses for each of the statements

13. .Sometimes it takes too much effort to speak	True	ρ
	False	ρ
14. I feel like I'm a burden to other people	True	ρ
	False	ρ
15. Travelling distances is difficult	True	ρ
	False	ρ
16. I don't like to be seen like this	True	ρ
	False	ρ
17. I feel like I'm losing my purpose in life	True	ρ
	False	ρ

18. I worry that I'm neglecting the people close to me — True ρ / False ρ

Please read each statement carefully and decide if it applies to you ***today***

19. I feel guilty asking for help — True ρ / False ρ

20. My condition limits the places I can go — True ρ / False ρ

21. I don't like having to rely on other people — True ρ / False ρ

22. I don't want to talk to anybody — True ρ / False ρ

23. I feel like I let people down — True ρ / False ρ

24. I'm reluctant to leave the house — True ρ / False ρ

25. I'm unable to participate in activities with my family and friends — True ρ / False ρ

END OF QUESTIONNAIRE: THANKS FOR YOUR ATTENTION

ECHOCARDIOGRAPHY

PULMONARY HYPERTENSION PARAMETERS (RANOLAZINE STUDY)

Patient Initials
Study Number

Parameters		Baseline	Week 12	Week 25	Week 48-52
Basal RV diameter (cm)					
Mid RV diameter (cm)					
Base to Apex Length (cm)					
RV fractional area change (%)					
TR max pressure gradient					
RA (pressure)					
RVSP (TRpg + RA pressure)					
PR end-diastolic velocity (PAPd)					
PADP (PR edv + RA pressure					
Free wall TDI					
TAPSE					
RV wall thickness					
3D full volume RV					
LV wall thickness (IVSd)					
LV wall thickness (PWd))					
LVED dimension					
LVES dimension					
LA volume					
RA dimension					
LVEF (biplane)					

Image Acquistion:

Apical 4-chamber (including LA, RA); Apical 4-chamber LV and 2-Chamber LV for biplane EF; Apical RV for dimensions TDI, and TAPSE; TR velocity; PR end diastolic velocity; IVC and RV (RVH).

Transthoracic Echo

1. The acquisition of images will strictly follow this protocol.
2. Echocardiographic examinations will be done at baseline and every six months over the next two years.
3. A standard 2D echocardiographic examination will be performed from the parasternal long and short axis views, apical 2, 4, and long axis views, and subcostal view. Attention should be paid to avoid foreshortening of the apical views. Intravenous myocardial contrast may be used to enhance endocardial border definition if necessary. Imaging should be performed with an ultrasound machine capable of Tissue Doppler imaging.
4. Optimize the overall 2D gain and Time Gain Compensation (TGC) settings to

optimize the 2D image. Each image should be optimized for the best endocardial definition to allow off line measurement of wall motion. Use harmonic imaging for endocardial border enhancement.
5. Supine blood pressure will be recorded at the end of the echo examination.
6. Digital acquisition as well as video backup will be collected of each view listed.