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RTA 402

402-C-1302

[redacted]

A DOSE-RANGING STUDY OF THE EFFICACY AND SAFETY OF BARDOXOLONE METHYL IN PATIENTS WITH PULMONARY HYPERTENSION

VERSION 7.0 – 26 JAN 2017

SPONSOR APPROVAL AND SIGNATURE PAGE

[redacted] Date

[redacted] Date

[redacted] Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for bardoxolone methyl. I have read the 402-C-1302 clinical study protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Medical and Scientific Leader	[redacted]	[redacted]
Clinical Study Manager	[redacted]	[redacted]
Medical Monitor	[redacted]	[redacted]
SAE Reporting	[redacted]	

2. SYNOPSIS

Name of Sponsor/Company:
Reata Pharmaceuticals, Inc.

Name of Investigational Product:
Bardoxolone methyl

Title of Study:
A Dose-Ranging Study of the Efficacy and Safety of Bardoxolone Methyl in Patients with Pulmonary Hypertension

Study center(s): Approximately 80 study centers

Studied period: 24-36 months Estimated date first patient enrolled: January 2014 Estimated date last patient completed: December 2018	**Phase of development:** 2

Objectives:
For patients enrolled in this study, the objectives are as follows:

Primary:

- To determine the recommended dose range for further study of bardoxolone methyl.

Secondary:

- To assess the change from baseline in 6-minute walk distance (6MWD) in those patients treated with bardoxolone methyl versus patients given placebo for 16 weeks.
- To assess the safety and tolerability of 16 weeks of treatment with bardoxolone methyl versus 16 weeks of administration of placebo.

Exploratory:

- To determine the effect of bardoxolone methyl in pulmonary hypertension (PH) associated with connective tissue disease, interstitial lung disease, and idiopathic etiologies, including subsets of patients with World Health Organization (WHO) Group III or WHO Group V PH.

Endpoints:

Efficacy:

Change from baseline in 6-minute walk distance (6MWD) through Week 16.

Safety:

Frequency, intensity, and relationship to study drug of adverse events and serious adverse events, concomitant medications, and change from baseline in the following assessments: physical examinations, vital sign measurements, 24-hour ambulatory blood pressure monitoring (ABPM; Cohorts 1 and 2 only), 12-lead electrocardiograms (ECGs), clinical laboratory measurements, and weight.

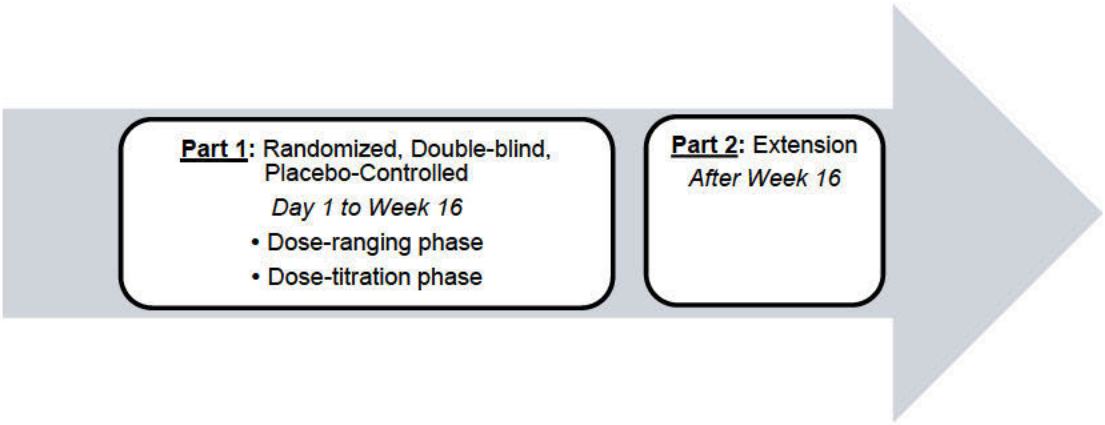
Exploratory:

[redacted]

[redacted]

Methodology:

This study consists of two parts: a 16-week double-blind, randomized, placebo-controlled treatment period ("Part 1"), followed by an extension period ("Part 2"). All patients who complete treatment in Part 1 may continue to Part 2. Within Part 1, the study consists of a dose-ranging phase and a dose-titration phase. Qualifying patients with PH in both the dose-ranging and dose-titration phases will be followed for safety, tolerability, and efficacy, and all patients enrolled in the study will follow a similar schedule of assessments.



Specified PH patient subtypes are defined as separate cohorts within the study to allow for independent assessment of safety, tolerability, and efficacy within each cohort.

The dose-ranging phase will evaluate two subtypes of PH patients:

- WHO Group I PAH patients with baseline 6MWD ≤ 450 m ("Cohort 1");
- WHO Group I PAH patients with baseline 6MWD > 450 m ("Cohort 2").

Based on information collected during the dose-ranging cohorts, an appropriate titration scheme will be identified and the study will transition to the dose-titration phase.

The dose-titration phase will evaluate two subtypes of PH patients:

- WHO Group I PAH patients with baseline 6MWD ≥ 150 m ("Cohort 3");
- Pulmonary hypertension associated with interstitial lung disease (PH-ILD) patients (i.e., select WHO Group III or V PH patients) with baseline 6MWD ≥ 150 m ("Cohort 4").

Within Cohort 3, two different subcohorts will be enrolled for independent assessment of safety, tolerability, and efficacy within each:

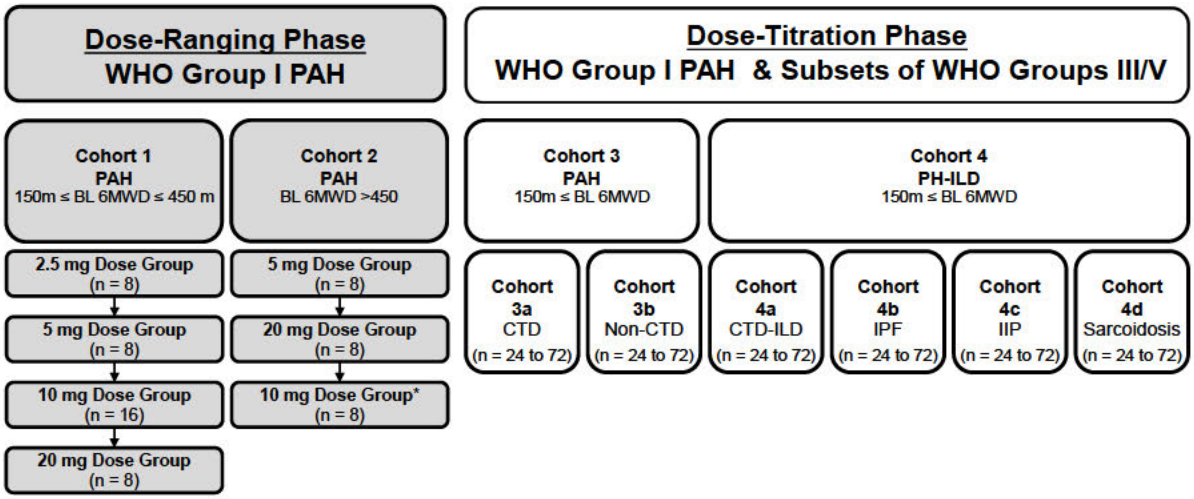
- Cohort 3a will consist of WHO Group I connective tissue disease (CTD)-PAH patients;
- Cohort 3b will consist of WHO Group I non-CTD PAH patients.

Given the heterogeneity of the PH-ILD patients, Cohort 4 is broken into four distinct subcohorts to allow for independent assessment of safety, tolerability, and efficacy within each:

- Cohort 4a will consist of WHO Group III PH patients with connective tissue disease associated interstitial lung disease (CTD-ILD);
- Cohort 4b will consist of WHO Group III PH patients with idiopathic pulmonary fibrosis;

- Cohort 4c will consist of WHO Group III PH patients with nonspecific interstitial pneumonia (NSIP) or selected idiopathic interstitial pneumonia (IIP) subtypes;
- Cohort 4d will consist of WHO Group V PH patients with sarcoidosis.

LARIAT Enrollment Cohorts within Study Phase



Part 1

Cohorts 1 and 2: In the dose-ranging phase of Part 1 of the study, up to two independently randomized cohorts may be opened at each dose level and patients will be allocated based on their baseline 6MWD (i.e., Cohort 1 for 6MWD ≤ 450 m and Cohort 2 for 6MWD > 450 m). Once opened for enrollment, each dose group will include the next eight eligible patients randomized using a 3:1 assignment ratio (bardoxolone methyl:placebo) to be administered once daily for 16 weeks. Within each cohort type, patients will be enrolled to one dose group at a time.

A Protocol Safety Review Committee (PSRC) will assess the starting dose of 2.5 mg and each new dose level of bardoxolone methyl for safety and tolerability based on review of all available data for this study at the time of each review. PSRC reviews will occur after the Week 4 data are available for the first eight patients enrolled at each new dose level combined across both Cohorts 1 and 2. The PSRC assessment will include a dose level recommendation for subsequent dose groups to escalate to a higher dose, proceed to a lower dose, or maintain the current dose. The PSRC may also recommend stopping dosing for current cohorts. Upon completion of dose ranging, the PSRC will continue to meet at regular intervals (approximately quarterly) to monitor safety of all enrolled patients.

Data from all patients enrolled in Cohort 1 (≤ 450 m patients) and Cohort 2 (> 450 m patients) will be used to provide information regarding the optimal dose range for evaluation of safety, tolerability, and efficacy, allowing the sponsor to select an appropriate dose of bardoxolone methyl for further evaluation in patients with WHO Group I PAH. Selecting from PSRC-recommended dose levels, the sponsor will determine the dose level for each subsequent dose group.

Cohorts 3 and 4: Cohort 3 and Cohort 4 will employ a dose titration scheme intended to identify an optimal dose for each patient. Cohort 3 includes additional WHO Group I patients, while Cohort 4 (PH-ILD cohort) allows only qualified WHO Group III or WHO Group V patients.

Cohort 3 will consist of two subcohorts, randomized independently within each subcohort using a 2:1 assignment ratio (bardoxolone methyl:placebo) to be administered once daily for 16 weeks:

- Cohort 3a will consist of WHO Group I connective tissue disease (CTD)-PAH patients;
- Cohort 3b will consist of WHO Group I non-CTD PAH patients.

Cohort 4 will consist of four subcohorts, randomized independently within each subcohort using a 2:1 assignment ratio (bardoxolone methyl:placebo) to be administered once daily for 16 weeks:

- Cohort 4a will consist of WHO Group III PH patients with connective tissue disease associated interstitial lung disease (CTD-ILD);
- Cohort 4b will consist of WHO Group III PH patients with idiopathic pulmonary fibrosis (IPF);
- Cohort 4c will consist of WHO Group III PH patients with nonspecific interstitial pneumonia (NSIP) or selected idiopathic interstitial pneumonia (IIP) subtypes;
- Cohort 4d will consist of WHO Group V PH patients with sarcoidosis.

Based on the variability in 6MWD change from baseline observed for the first 24 patients enrolled in each subcohort of Cohort 3 and Cohort 4, the Sponsor may choose to increase the number of patients within each subcohort to a maximum of 72 patients. For Cohort 3b, a maximum of approximately 24 patients may be enrolled from the United States.

Patients in Cohorts 3 and 4 will start at 5 mg (or placebo) and will dose escalate to 10 mg at Week 4 unless a dose-limiting toxicity (DLT) is reported (Section 7.3.1). Identification of DLTs is left to the discretion of the Investigator and may include clinically important changes from baseline in BNP, clinical signs of fluid retention, or other adverse events. Suspected DLTs should be discussed with the medical monitor prior to changing dose. If at any time the patient reports an AE that the Investigator considers to be a DLT, the Investigator may choose to decrease the patient's dose to one-half of the prior dose (e.g., 10 mg to 5 mg). Dose de-escalation can occur more than once, but dose reduction is not permitted below a dose of 2.5 mg. Dose escalation during Part 1 is permitted for all patients at Week 4 only.

All patients in Part 1 of the study (i.e., Cohorts 1, 2, 3a-b, and 4a-d) will follow similar visit and assessments schedules. Selected assessments [redacted]) will be optional for all enrolled patients at Sponsor-qualified sites. Other assessments (e.g., ABPM, [redacted]) conducted for Cohorts 1 and 2 will not be conducted for patients in Cohorts 3 and 4. Following randomization, patients will be assessed in person during treatment at Weeks 1, 2, 4, 8, 12, and 16 and by telephone contact on Days 3, 10, and 21. Patients enrolling in Cohorts 3 and 4 will have additional assessments in person at Week 6 and additional telephone contact on Days 31, 38, and 49. Patients who do not enter Part 2 of the study (i.e., the extension period), either because they have discontinued taking study drug during Part 1 or have completed the 16-week treatment period as planned but chosen not to continue to Part 2 of the study, will complete an end-of-treatment visit when patient ends study drug. In addition, a follow-up visit should occur four weeks after the date of administration of the last dose of study drug.

Part 2 (extension period):

Patients who discontinue treatment prematurely in study Part 1 are not eligible to continue into study Part 2. All patients from Part 1 who complete the 16-week treatment period as planned will be eligible to continue directly into the extension period to evaluate the intermediate and long-term safety and efficacy of bardoxolone methyl. Day 1 of the extension period will be the same as the Week 16 visit for the treatment period.

Cohort 1 and Cohort 2 patients randomized to placebo in Part 1 of the study will be assigned to receive bardoxolone methyl at their group-specific dose in the extension period. Patients enrolled in Cohorts 1 and 2 may dose titrate to the 10 mg dose or de-escalate (minimum dose of 2.5 mg) at

scheduled or unscheduled visits. However, patients who dose escalate must have a telephone call 1 week after dose escalation and an unscheduled office visit or a home health visit 2 weeks (±3 days) after dose escalation to collect clinical chemistry, BNP, and NT-Pro BNP.

Cohort 3 and 4 patients randomized to placebo in study Part 1 will be assigned to 5 mg of bardoxolone methyl, whereas, patients randomized to bardoxolone methyl in study Part 1 will begin study Part 2 (Week 16) at the same dose of bardoxolone methyl as they ended with in study Part 1. All patients in Cohorts 3 and 4 will have the option to up-titrate their dose at the Week 20 visit, and may de-escalate in dose (minimum dose of 2.5 mg) at scheduled or unscheduled visits. Treatment assignment will remain blinded for Cohort 3 and 4 patients through Week 20.

Treatment-compliant patients who have completed Part 2 of the study are eligible to continue receiving bardoxolone methyl through an extended access program (Study 402-C-1602). After Week 32, visits will occur every 24 weeks until bardoxolone methyl is available through the extended access program. Once bardoxolone methyl is available through the extended access program, patients in Part 2 who have completed at least 32 weeks of the study will complete an End of Treatment Visit.

Number of patients (planned):

Approximately 198 patients are expected to be enrolled in Part 1 of the study (38 patients in Cohort 1; 16 patients in Cohort 2; and approximately 24 patients in each of Cohorts 3a-b and 4a-d). Based on the variability in 6MWD observed in Cohorts 3 and 4, the Sponsor may choose to increase the number of patients to a maximum of 72 patients in each of Cohorts 3a-b and 4a-d. Variability for each subcohort will be assessed separately. The maximum number of patients enrolled will be 486.

All eligible patients from Part 1 will be included in Part 2, and no new patients will be randomized to Part 2 of the study.

Diagnosis and main criteria for inclusion:

1. Adult male and female patients ≥ 18 to ≤ 75 years of age upon study consent;
2. BMI > 18.5 kg/m^2;
3. Symptomatic pulmonary hypertension WHO Functional Class II and III;
4. WHO Group I, III, or V PH according to the following criteria:
    a. If diagnosed with WHO Group I PAH, then one of the following subtypes:
        i. Idiopathic or heritable PAH;
        ii. PAH associated with connective tissue disease;
        iii. PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following shunt repair;
        iv. PAH associated with anorexigen or drug-induced toxicity;
        v. PAH associated with human immunodeficiency virus (HIV); or
    b. If WHO Group III PH, then primary diagnosis must be one of the following subtypes:
        i. Connective tissue disease associated ILD (CTD-ILD);

ii. Idiopathic pulmonary fibrosis (IPF) according to the American Thoracic Society and European Respiratory Society (ATS/ERS) guidelines (Raghu 2011);

iii. Nonspecific interstitial pneumonia (NSIP) or the following idiopathic interstitial pneumonia subtypes, according to the American Thoracic Society and European Respiratory Society (ATS/ERS) guidelines (Travis 2013):

1. Respiratory bronchiolitis-associated interstitial lung disease;
2. Desquamative interstitial pneumonia;
3. Cryptogenic organizing pneumonia;
4. Acute interstitial pneumonitis;
5. Idiopathic lymphoid interstitial pneumonia;
6. Idiopathic pleuroparenchymal fibroelastosis;
7. Unclassifiable idiopathic interstitial pneumonia, including patients who have not had a lung biopsy; or

c. If WHO Group V PH, then patient must be diagnosed with sarcoidosis;

5. Had a diagnostic right heart catheterization performed and documented prior to Day 1 that confirmed a diagnosis of PH according to all the following criteria:

a. If diagnosed with WHO Group I PAH, then:

i. Mean pulmonary artery pressure ≥ 25 mm Hg (at rest);

ii. Pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg;

iii. Pulmonary vascular resistance > 240 dyn.sec/cm^5 or > 3 mm Hg/Liter (L)/minute;

b. If not diagnosed with WHO Group I PAH, then:

i. Mean pulmonary artery pressure ≥ 21 mm Hg (at rest);

ii. Pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg;

iii. Pulmonary vascular resistance > 160 dyn.sec/cm^5

6. Has BNP level ≤ 400 pg/mL;

7. Has an average 6-minute walk distance (6MWDs) ≥ 150 meters on two consecutive tests performed on different days prior to randomization, with both tests measuring within 15% of one another;

8. Has been receiving no more than two (2) approved disease-specific PAH therapies. Cohort 3b WHO Group I PAH patients enrolled outside the United States must be receiving zero (0) or one (1) PAH therapies. PAH therapy must be at a stable dose for at least 90 days prior to Day 1;

9. If WHO Group III or WHO Group V, disease-specific therapy must be at a stable dose for 30 days;
10. Has maintained a stable dose for 30 days prior to Day 1 if receiving any of the following therapies that may affect PH: vasodilators (including calcium channel blockers), digoxin, L-arginine supplementation, or oxygen supplementation;
11. If receiving prednisone, has maintained a stable dose of ≤ 20 mg/day (or equivalent dose if other corticosteroid) for at least 30 days prior to Day 1. If receiving treatment for connective tissue disease (CTD) with any other drugs, doses should remain stable for the duration of the study;
12. Had pulmonary function tests (PFTs) within 90 days prior to Day 1 that meet the following criteria:
    a. For WHO Group I PAH patients with connective tissue disease, total lung capacity (TLC) ≥ 65% (predicted);
    b. For all other WHO Group I PAH patients,
        i. Forced expiratory volume in 1 second (FEV1) ≥ 65% (predicted); or
        ii. FEV1/forced vital capacity ratio (FEV1/FVC) ≥ 65%;
    c. For WHO Group III or V PH patients, total lung capacity (TLC) between 50-90% (predicted);
13. For WHO Group I patients, had a ventilation-perfusion (V/Q) lung scan, spiral/helical/electron beam computed tomography (CT) or pulmonary angiogram prior to Screening that shows no evidence of thromboembolic disease (i.e., should note normal or low probability for pulmonary embolism). If V/Q scan was abnormal (i.e., results other than normal or low probability), then a confirmatory CT or selective pulmonary angiography must exclude chronic thromboembolic disease;
14. Has adequate kidney function defined as an estimated glomerular filtration rate (eGFR) ≥ 45 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) 4-variable formula;
15. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures;
16. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study prior to initiation of any patient-mandated procedures;
17. For WHO Group III or V PH patients, the presence of ILD must be confirmed by a diagnostic high resolution computed tomography (HRCT) scan or biopsy performed and documented prior to Day 1.

Major exclusion criteria:

1. Participation in other investigational clinical studies involving pharmaceutical products being tested or used in a way different from the approved form or when used for an unapproved indication within 30 days prior to Day 1;

2. Initiation of an exercise program for cardio-pulmonary rehabilitation within 3 months (90 days) prior to Day 1 or planned initiation during Part 1 of the study;
3. Stopped receiving any PH chronic therapy within 60 days prior to Day 1;
4. Requirement for receipt of intravenous inotropes within 30 days prior to Day 1;
5. Has uncontrolled systemic hypertension as evidenced by sitting systolic blood pressure (BP) > 160 mm Hg or sitting diastolic blood pressure > 100 mm Hg during Screening after a period of rest;
6. Has systolic BP < 90 mm Hg during Screening after a period of rest;
7. WHO Group III patients with pulmonary hypertension primarily associated with chronic obstructive pulmonary disease, sleep-disordered breathing, and/or alveolar hypoventilation disorders;
8. WHO Group III or V patients who at rest require supplemental oxygen at a rate > 4 L/min or have peripheral capillary oxygen saturation (SpO2) levels < 92%;
9. Has a history of clinically significant left-sided heart disease and/or clinically significant cardiac disease, including but not limited to any of the following:
    a. Congenital or acquired valvular disease if clinically significant apart from tricuspid valvular insufficiency due to pulmonary hypertension;
    b. Pericardial constriction;
    c. Restrictive or congestive cardiomyopathy;
    d. Left ventricular ejection fraction < 40% per echocardiogram (ECHO) within 60 days of Day 1;
    e. Any current or prior history of symptomatic coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or anginal chest pain);
10. Clinical instability within 8 weeks prior to Day 1, such as hospitalization due to respiratory or cardiac symptoms, acutely decompensated heart failure, syncope, or other events that in the investigator's opinion would suggest the patient is an inappropriate candidate for the study;
11. Has more than two of the following clinical risk factors for left ventricular diastolic dysfunction:
    a. Age > 65 years;
    b. BMI $\geq$ 30 kg/m^2;
    c. History of systemic hypertension;
    d. History of type 2 diabetes;
    e. History of atrial fibrillation;
12. History of atrial septostomy within 180 days prior to Day 1;

13. Obstructive sleep apnea that is untreated;
14. For patients with HIV-associated PAH, any of the following:
    a. Concomitant active opportunistic infections within 180 days prior to Screening;
    b. Detectable viral load within 90 days prior to Screening;
    c. Cluster designation 4 (CD4+) T-cell count < 200 mm^3 within 90 days prior to Screening;
    d. Changes in antiretroviral regimen within 90 days prior to Screening;
    e. Using inhaled pentamidine;
15. Has a history of portal hypertension or chronic liver disease, including hepatitis B and/or hepatitis C (with evidence of recent infection and/or active virus replication) defined as mild to severe hepatic impairment (Child-Pugh Class A-C);
16. Serum aminotransferase (ALT or AST) levels > 1.5X the upper limit of normal (ULN) at Screening;
17. Hemoglobin (Hgb) concentration < 10.5 g/dL at Screening;
18. Diagnosis of Down syndrome;
19. History of malignancy within 5 years prior to screening, with the exception of localized skin or cervical carcinomas;
20. Active bacterial, fungal, or viral infection, incompatible with the study;
21. Known or suspected active drug or alcohol abuse, per Investigator judgment;
22. Major surgery within 30 days prior to Screening or planned to occur during the course of the study;
23. Unwilling to practice methods of birth control (both males who have partners of childbearing potential and females of childbearing potential) during screening, while taking study drug and for at least 30 days after the last dose of study drug is ingested;
24. Women who are pregnant or breastfeeding;
25. Any disability or impairment that would prohibit performance of the 6MWT;
26. Any abnormal laboratory level that, in the opinion of the Investigator, would put the patient at risk by trial enrollment;
27. Patient is, in the opinion of the Investigator, unable to comply with the requirements of the study protocol or is unsuitable for the study for any reason;
28. Known hypersensitivity to any component of the study drug;
29. Unable to communicate or cooperate with the Investigator due to language problems, poor mental development, or impaired cerebral function;
30. Use of intravenous (iv) or subcutaneous (sc) prostacyclin/prostacyclin analogues;
31. Prior exposure to bardoxolone methyl.

Investigational product, dosage and mode of administration:

Bardoxolone methyl (2.5, 5, 10, 20 mg) will be administered orally once daily in the morning.

Duration of treatment:

Part 1: Bardoxolone methyl or placebo will be administered once a day in the morning for 16 weeks.

Part 2: Bardoxolone methyl will be administered once a day in the morning for the duration of extension period.

Reference therapy, dosage and mode of administration:

Part 1: Placebo will be administered orally once a day in the morning for 16 weeks.

Part 2: Not applicable.

Criteria for evaluation:

Efficacy: Changes from baseline in 6MWD; [redacted]

Safety: Results of physical examinations, laboratory results (clinical chemistry, hematology, urinalysis), 24-hour ABPM results (Cohorts 1 and 2 only), vital sign measurements, ECG results, concomitant medications, adverse events, and serious adverse events.

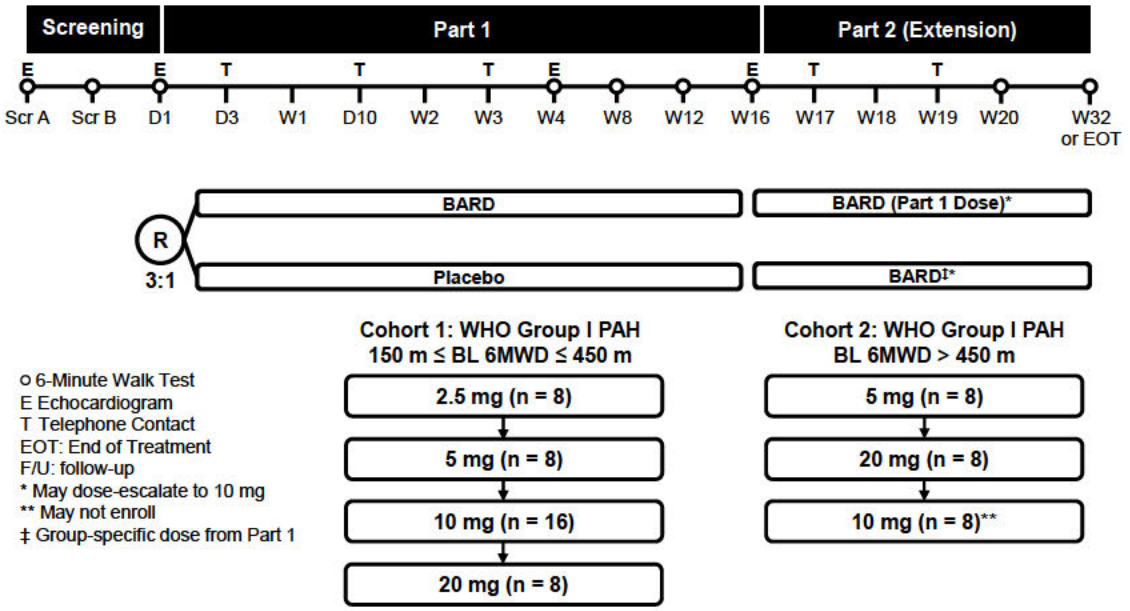
Pharmacokinetics: Bardoxolone methyl plasma concentration-time data, metabolite concentration-time data (if available), and estimated pharmacokinetic parameters for each analyte.

Statistical methods:

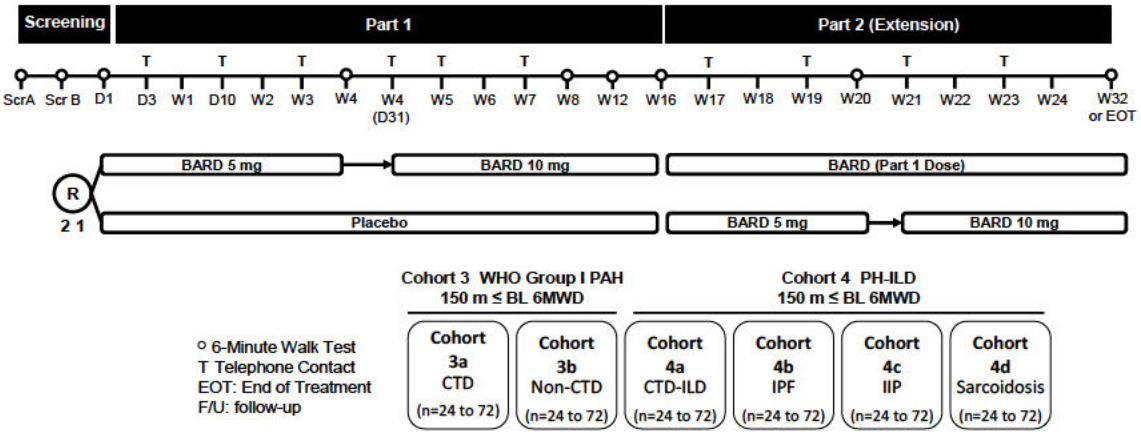
Sample size: A sample size of 8 patients randomized at a 3:1 (bardoxolone methyl:placebo) assignment ratio in each dose group (Cohorts 1 and 2) includes 6 patients treated with bardoxolone methyl for identification of gross safety signals. A small number of patients at each dose is not expected to fully characterize safety, therefore issues of concern identified in only 1 of 6 patients (16%) treated with bardoxolone methyl may suggest the need to collect additional information before escalating the dose, by either adding another cohort at the current dose level or at a lower dose as determined by the PSRC. Enrollment of patients at each additional dose level adds 6 more patients treated with bardoxolone methyl to further characterize safety, tolerability, and efficacy.

[redacted]

Schema for Cohorts 1 and 2 Patients in the LARIAT Study



Schema for Cohorts 3 and 4 Patients in the LARIAT Study



All patients from Part 1 who complete the 16-week treatment period according to the protocol will be eligible to continue in the extension phase (Part 2) of the study.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
6MWD	6-minute walk distance
6MWT	6-minute walk test
AE	Adverse event
ABPM	Ambulatory blood pressure monitoring
ACA	Anti-centromere
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Anti-nuclear
Anti-RNAP	Anti-RNA polymerase enzyme
Anti-U1RNP	Anti-U1 nuclear ribosome
Anti-U3RNP	Anti-U3 nuclear ribosome
Anti-Th/To	Anti-ribonucleoprotein
Anti-Ds-DNA	Anti-double stranded DNA
AST	Aspartate aminotransferase
(ATS/ERS)	American Thoracic Society and European Respiratory Society
aPTT	Activated partial thromboplastin time
AUC	Area under the plasma concentration time curve
BMI	Body mass index
BNP	B-type natriuretic peptide
BSA	Body surface area
BUN	Blood urea nitrogen
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CFR	Code of Federal Regulations (US)
CKD	Chronic kidney disease
CPET	Cardiopulmonary Exercise Testing
CPK	Creatine phosphokinase
CT	Computed tomography
CTD	Connective Tissue Disease

Abbreviation or Specialist Term	Explanation
CTD-ILD	Connective tissue disease associated with interstitial lung disease
CWE	Clinical Worsening Event
DL_{CO}	Diffusion capacity of lung for carbon monoxide
DLT	Dose-limiting toxicity
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ERA	Endothelin receptor antagonist
FDA	Food and Drug Administration (US)
FEV_1	Forced expiratory volume
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GLP	Good laboratory practice
HDL-C	High density lipoprotein cholesterol
HDPE	High-density polyethylene
HED	Human equivalent dose
HIV	Human immunodeficiency virus
HRCT	High-resolution computed tomography
ICH	International Conference on Harmonization
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease
INR	International normalized ratio
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LDL-C	Low density lipoprotein cholesterol
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration

Abbreviation or Specialist Term	Explanation
MCV	Mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MDSC	Myeloid derived suppressor cells
MRI	Magnetic resonance imaging
MRSD	Maximum recommended starting dose
MUGA	Multiple Gated Acquisition Scan
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B-cells
NIRS	Near-infrared spectroscopy
Nrf2	Nuclear factor (erythroid-derived 2)-related factor 2
NO	Nitric oxide
NOAEL	No observed adverse effect level
NSIP	Nonspecific interstitial pneumonia
NT-Pro BNP	N-Terminal Pro-Brain Natriuretic Peptide
PAH	Pulmonary arterial hypertension
PBMC	Peripheral blood mononuclear cell
PCWP	Pulmonary capillary wedge pressure
PGC1α	Peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1 alpha
PET/HRCT	Positron emission tomography/high resolution computed tomography
PH	Pulmonary hypertension
PH-ILD	Pulmonary hypertension associated with interstitial lung disease
PI	Principal Investigator
PK	Pharmacokinetic
PSRC	Protocol Safety Review Committee
PT	Prothrombin time
PTT	Partial thromboplastin time
Qd	Once daily
RBC	Red blood cell
RHC	Right heart catheterization
ROS	Reactive oxygen species
RNS	Reactive nitrogen species

Abbreviation or Specialist Term	Explanation
SAE	Serious adverse event
SAP	Statistical analysis plan
STD10	Rodent severely toxic dose in 10% of animals
TAM	Tumor associated macrophages
TBL	Total bilirubin
ULN	Upper limit of normal
US	United States
VLDL-C	Very low density lipoprotein
WBC	White blood cell
WOCBP	Women of child bearing potential

5. INTRODUCTION

Bardoxolone methyl and its analogs are oleanolic acid-derived synthetic triterpenoid compounds that potently induce the Nrf2-Keap1 pathway (Wu 2011; Rojas-Rivera 2012). Through interaction with the Nrf2 repressor molecule, Keap1, bardoxolone methyl and its analogs promote translocation of Nrf2 to the nucleus, where it binds to antioxidant response elements in the promoter region of its target genes, leading to induction of many antioxidant and cytoprotective enzymes and related proteins (Lee 2009; Dinkova-Kostova 2005). Bardoxolone methyl and its analogs are also potent inhibitors of the NF-κB inflammatory pathway through both direct (i.e., inhibition of IKKβ kinase activity) and indirect mechanisms (i.e., detoxification of reactive oxygen species) (Osburn 2008). Because of this dual mechanism of action, bardoxolone methyl and its analogs are hypothesized to have potential therapeutic relevance in a variety of disease settings involving oxidative stress and inflammation.

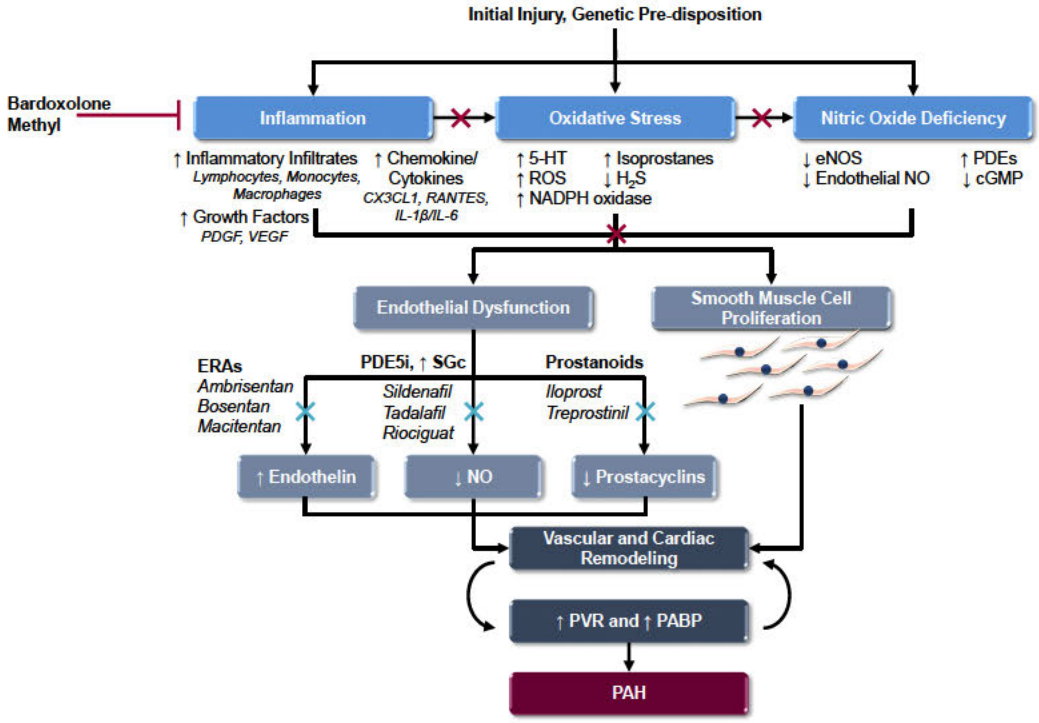
Because of the importance of NF-κB in the growth, invasion, and metastasis of tumors, bardoxolone methyl was initially studied in cancer. Bardoxolone methyl has been shown to induce differentiation, inhibit proliferation, and induce apoptosis in cancer cell lines (Hong 2012). Potent single-agent activity has been observed in several animal models of cancer with significant inhibitory effects on tumor growth (Place 2003; Deeb 2012), metastasis (Deeb 2012), and angiogenesis (Valcarcel-Ares 2012). In a first-in-human study in patients with relapsed and refractory metastatic solid tumors and lymphoid malignancies, bardoxolone methyl was shown to significantly increase Nrf2 target genes in peripheral blood mononuclear cells (PBMCs) and significantly reduce NF-κB and cyclin D1 levels in biopsies from patients. In addition to the objective responses and disease stabilization that were noted, improvements in estimated glomerular filtration rate (eGFR) were observed that appeared to correlate with the level of kidney dysfunction.

Because of the noted improvements in eGFR in cancer patients, bardoxolone methyl and analogs have been studied in the setting of kidney disease. Bardoxolone methyl analogs inhibit angiotensin II-induced reductions in volume of intact glomeruli and increase directly-measured GFR (inulin clearance) in rodent models of chronic kidney disease (CKD). In the 5/6 nephrectomy model of chronic renal failure, a bardoxolone methyl analog improved renal function, reduced plasma lipid peroxidation, and restored normal endothelial function. Seven studies have been conducted in patients with CKD and type 2 diabetes. In all studies, treated patients achieved marked improvements in renal function as determined by changes in eGFR, BUN, phosphorus, and uric acid. Improvements in creatinine clearance and markers of endothelial dysfunction were also noted in studies that assessed these parameters. In the largest study, conducted in Stage 4 CKD patients (eGFR 15 – 29 mL/min/1.73 m^2) with type 2 diabetes, a subset of patients with elevated baseline BNP and history of heart failure were shown in post hoc analyses to be at risk for fluid retention. Mechanistic studies subsequently identified modulation of the endothelin pathway as the likely pharmacologic effect that precipitated fluid retention in this subset of patients at risk.

As the risk factors for fluid retention with bardoxolone methyl are similar to those with endothelin receptor antagonists (ERAs), risk mitigation features, including appropriate eligibility criteria, will be used to reduce the risk of fluid retention in subsequent studies. The bardoxolone methyl-mediated hemodynamic effects on renal function, which preclinical data support are

caused by improvements in endothelial dysfunction and suppression of smooth muscle cell contraction, are also relevant to PH.

The molecular and pharmacologic effects of bardoxolone methyl are broad through its induction of Nrf2 and suppression of NF-κB. Bardoxolone methyl may therefore address multiple facets of the pathophysiology of PAH because it suppresses activation of pro-inflammatory mediators, reduces pathologic endothelin signaling, enhances endothelial nitric oxide (NO) bioavailability, suppresses vascular proliferation, and prevents maladaptive remodeling. Furthermore, while existing therapies primarily target only smooth muscle cells, bardoxolone methyl targets multiple cell types relevant to PH, including endothelial cells, smooth muscle cells, and macrophages. Of note, recent evidence demonstrates that genetic or pharmacologic induction of Nrf2, the molecular target of bardoxolone methyl, suppresses formation of the PH phenotype in a mouse model of hypoxic pulmonary hypertension (Eba 2013).

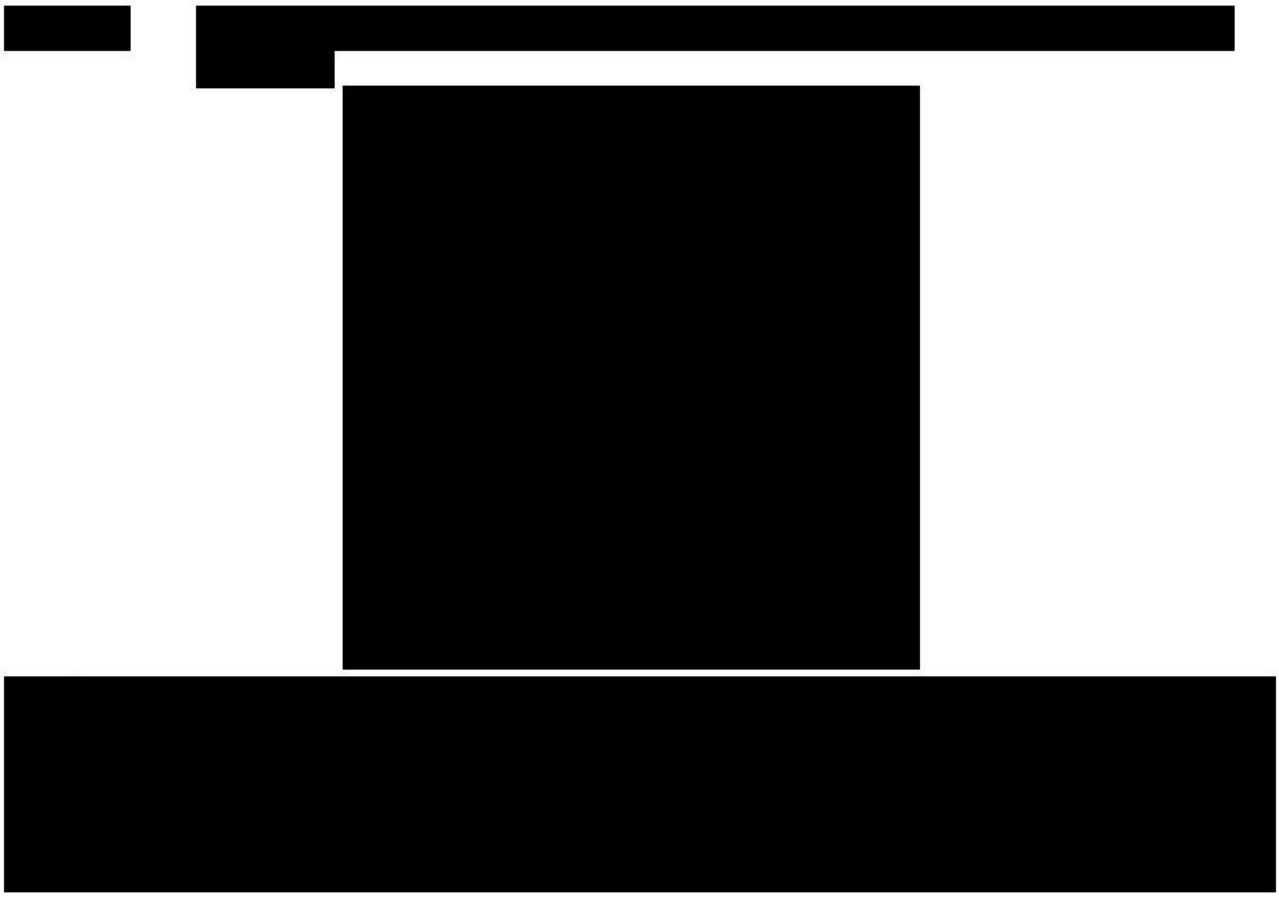


Additionally, an emerging concept in the pathogenesis of pulmonary hypertension is the role of metabolic dysfunction as a major cause of reduced exercise capacity and fatigue, as well as in disease progression. A high frequency of insulin resistance and metabolic syndrome-like features have been described in patients with PH, and glucose intolerance is associated with a decrease in 6MWD (Pugh 2011). Pulmonary hypertension patients have decreased ATP production due to a chronic shift from mitochondrial respiration to glycolysis (Sutendra 2014). Ultimately, the chronic shift from mitochondrial respiration to glycolysis leads to skeletal muscle dysfunction and impaired exercise capacity (Mainguy 2010; Batt 2014). Indeed, the skeletal muscle within pulmonary hypertension patients displays a decreased expression of mitochondrial respiration enzymes, defects in mitochondrial oxidative phosphorylation, and impairments in mitochondrial biogenesis (Batt 2014; Malenfant 2015). Moreover, preclinical pulmonary hypertension models have demonstrated that peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α), a central inducer of mitochondrial biogenesis, is decreased within

the skeletal muscle, resulting in impaired skeletal muscle fiber function (Vescovo 2005). Overall, these defects in skeletal muscle contribute to muscle weakness and fatigue, as well as impaired exercise capacity in pulmonary hypertension patients (Batt 2014).

Several lines of evidence suggest that Nrf2 activation can increase mitochondrial respiration and biogenesis, in addition to inducing expression of numerous antioxidative genes to counter reactive oxygen species (ROS). Specifically, by increasing the availability and production of reducing equivalents such as NADH and $FADH_2$, Nrf2 activation improves mitochondrial ATP production and improves the efficiency of mitochondrial respiration and oxygen consumption. In addition, Nrf2 activation results in improved beta-oxidation of fatty acids and improved uptake of glucose, which leads to improvement in mitochondrial respiration, oxygen consumption, and energy production. Furthermore, Nrf2-mediated induction of PGC1α, a master transcriptional coactivator and central inducer of mitochondrial biogenesis, by bardoxolone methyl is hypothesized to increase mitochondrial biogenesis and energy production.

Approved PH therapies act to promote vasodilation of pulmonary arteries and through reductions in pulmonary resistance and right-sided cardiac pressure, these therapies have indirect effects on vascular and cardiac remodeling. Given the degree of parenchymal and vascular fibrosis and remodeling in interstitial lung disease (ILD) patients, vasodilation therapies are minimally effective in treating pulmonary hypertension in those patients. Notably, none of the approved therapies target the metabolic and mitochondrial dysfunction. [redacted] Approved PAH therapies tested have no significant effects on the tested parameters of mitochondrial function. Thus, bardoxolone methyl may provide a novel approach to PH therapy through improvements in bioenergetics and mitochondrial function that translate to increased muscular function and exercise capacity in PH patients, including those with interstitial lung disease.



From a safety perspective, apart from fluid retention observed in advanced CKD patients with specific risk factors, bardoxolone methyl appears to possess a favorable clinical safety profile compared to existing PAH therapies. Bardoxolone methyl does not have primary systemic hemodynamic depressor effects and is therefore unlikely to promote systemic hypotension or syncope. The available preclinical and clinical data also indicate that bardoxolone methyl does not cause liver toxicity. A nonhuman primate developmental toxicity study of bardoxolone methyl demonstrated no adverse effects on embryo-fetal development.

Thus, the established pharmacologic effects of bardoxolone methyl are directly applicable to the treatment of PH in WHO Group I patients and select WHO Group III and V patients. Given the nonclinical and clinical evidence supporting potential efficacy of bardoxolone methyl in PH, the Sponsor proposes a clinical study to test bardoxolone methyl in patients with PH.

5.1. Clinical Experience with Bardoxolone Methyl

Approximately 1950 individuals have been exposed to bardoxolone methyl. Sixteen studies have been completed (seven in patients with CKD and type 2 diabetes, four in non-CKD indications, and five in healthy subjects).

5.1.1. Safety and Tolerability

Please refer to the Investigator's Brochure for a detailed discussion of safety findings for studies in healthy subjects, and non-CKD and CKD patients with bardoxolone methyl.

5.1.2. Fluid Overload

Similar to ERAs in certain patient populations, including bosentan in advanced congestive heart failure and avosentan in advanced CKD, bardoxolone methyl treatment was found to be associated with an increased risk for fluid overload and heart failure hospitalizations in the BEACON trial, which enrolled patients with Stage 4 CKD (eGFR 15-29 mL/min/1.73 m^2) and type 2 diabetes. The overall increased risk for fluid overload and heart failure events with bardoxolone methyl appeared to be limited to the first three to four weeks after initiation of treatment. Elevated BNP and prior hospitalization for heart failure were identified as risk factors that contributed to increased risk for these events. The increased risk for these events from bardoxolone methyl treatment had not been observed in six previous CKD studies, which were mostly conducted in patients with Stage 3b CKD (eGFR 30-44 mL/min/1.73 m^2), patients with hepatic dysfunction, cancer patients, or healthy volunteers.

Review of admission notes and narrative descriptions for heart failure hospitalizations in BEACON indicates that heart failure in bardoxolone methyl-treated patients was often preceded by rapid fluid weight gain (several kilograms within the first weeks of treatment initiation) and was not associated with acute renal decompensation or acutely reduced left ventricular contractility. Available data from BEACON and other studies suggest that bardoxolone methyl treatment can differentially affect hemodynamic status according to the clinical condition of patients and likely promotes fluid retention in patients with more advanced renal dysfunction and other recognized risk factors associated with heart failure at baseline. This current study will employ risk mitigation procedures to reduce the potential for bardoxolone methyl-induced fluid overload, including exclusion of patients with the identified risk factors and close monitoring for fluid retention within the first month of treatment.

5.1.3. Transaminase and GGT Elevations

In clinical studies of bardoxolone methyl, almost all patients had increases of transaminase enzymes above baseline upon initiation of treatment, which followed a consistent pattern and have not been associated with elevations in bilirubin or other signs of liver toxicity. In BEACON, fewer hepatobiliary SAEs were observed in the bardoxolone methyl arm than in the placebo arm. The elevations begin immediately after initiation of treatment or an increase in dose and peak approximately two to four weeks later. In most patients, transaminase elevations were mild, but approximately 4 to 11% of patients experienced an elevation to greater than three times the ULN. The elevations resolved to levels less than the ULN in most all patients with elevations, within two weeks after peak values while patients continued taking study drug. Patients who experienced elevations to greater than three times the ULN sometimes required additional time to resolve. While some patients have had elevations to above three times the ULN, persistent elevations to above three times the ULN have not been observed, and the elevations did not recur once resolved, unless caused by other factors.

Bardoxolone methyl regulates GGT, a known Nrf2 target gene. In clinical studies, low level GGT elevations during treatment were common, mild, and typically lasted longer than ALT/AST elevations. Bilirubin levels in patients experiencing transaminase or GGT elevations due to treatment with bardoxolone methyl either remained at baseline levels or decreased. The ALT, AST, and GGT elevations were generally self-limiting in patients who continued treatment with study drug.

5.1.4. Muscle Spasms

Muscle spasm was the most frequently reported adverse event in clinical trials of bardoxolone methyl in patients with CKD and type 2 diabetes. The muscle spasms most often manifested in the first two months of treatment and resolved spontaneously or with empirical treatment. They occurred mostly at night, in the lower extremities, and were generally mild to moderate in severity. Muscle spasms may result from improved insulin sensitivity and glucose uptake in skeletal muscle cells. Increases in glucose uptake, as assessed by the hyperinsulinemic-euglycemic clamp procedure, were observed in response to bardoxolone methyl in a subset of patients enrolled in a phase 2a study. Increases in the whole-body glucose disposal rate were observed in mice treated with bardoxolone methyl, as well. Increased glucose uptake was observed in isolated calf muscles of the mice, but not in white adipose tissue (Saha 2010). To date, in those cases where serum creatinine phosphokinase (CPK) levels have been measured, no association has been observed between muscle spasms and elevated CPK levels in patients treated with bardoxolone methyl. Clinical signs and laboratory findings associated with the reports of muscle spasms have not been consistent with muscle toxicity. Bardoxolone methyl subjects showed no increase in prominent laboratory findings associated with muscle toxicity, such as increased levels of serum markers, including creatinine, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), uric acid, phosphorus, and potassium, which were monitored weekly during the first two months of a prior study (BEAM) when muscle spasms were most frequently reported.

5.1.5. Weight Loss

Decreases in weight and reports of anorexia/decreased appetite have been observed following treatment with bardoxolone methyl in patients with CKD and type 2 diabetes. In the studies of patients with CKD and type 2 diabetes, 17% of bardoxolone methyl patients reported the adverse events of weight decrease or decreased appetite (irrespective of relationship to treatment). Weight reduction was more pronounced in patients treated with bardoxolone methyl than in those given placebo.

Weight loss of approximately one kilogram per month was observed, with patients of higher body-mass index at baseline losing more than those of normal or moderately-elevated body-mass index. Patients who reported taste-related adverse events had more weight loss.

5.1.6. Hypomagnesaemia

Hypomagnesaemia was reported as an adverse event for 15.5% of patients with CKD and type 2 diabetes who received bardoxolone methyl. The adverse event of hypomagnesaemia (of any relationship) was more frequently reported in bardoxolone methyl-treated patients than in patients given placebo. The Investigators considered almost all reported events to be mild. Additionally, patients treated with bardoxolone methyl had a greater decrease from baseline in serum magnesium levels than patients given placebo; the decrease was evident within 4 weeks and attenuated after 8 weeks of starting therapy. In bardoxolone methyl clinical studies performed to date, a post-hoc analysis identified no correlation between hypomagnesaemia and either gastrointestinal adverse events or cardiac adverse events, including cardiac dysrhythmias and prolonged QTc. The 24-hour urine collections from the BEACON ambulatory blood pressure monitoring sub-study did not show an increase in urinary magnesium levels, indicating

that renal loss of magnesium did not account for the reductions in serum magnesium observed with bardoxolone methyl treatment in CKD patients. Notably, in a thorough QT study that tested doses of bardoxolone methyl up to 80 mg, bardoxolone methyl did not increase the QT interval.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

For patients enrolled in this study, the objectives are as follows:

- Primary objective
  - To determine the recommended dose range for further study of bardoxolone methyl.
- Secondary objectives
  - To assess the change from baseline in 6-minute walk distance (6MWD) in those patients treated with bardoxolone methyl versus patients given placebo for 16 weeks.
  - To assess the safety and tolerability of 16 weeks of treatment with bardoxolone methyl versus 16 weeks of administration of placebo.
- Exploratory objectives
  - To determine the effect of bardoxolone methyl in pulmonary hypertension associated with connective tissue disease, interstitial lung disease and idiopathic etiologies including subsets of patients with WHO Group III or WHO Group V PH.

6.2. Endpoints

6.2.1. Primary Efficacy Endpoint

Change from baseline in 6MWD through Week 16.

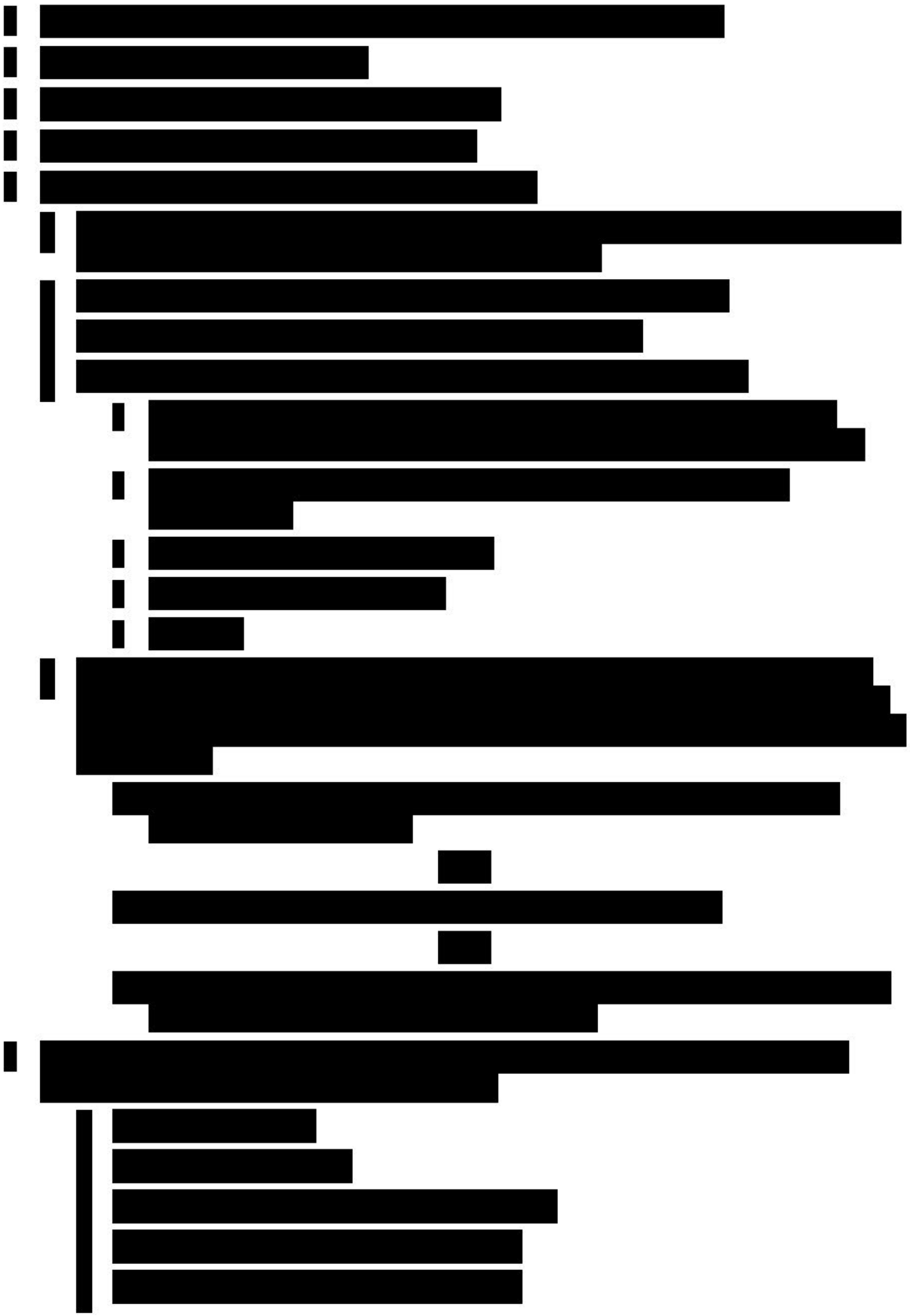
6.2.2. Safety Endpoints

Frequency, intensity, and relationship to study drug of adverse events and serious adverse events, concomitant medications, and change from baseline in the following assessments:

- Physical examinations;
- Vital sign measurements;
- 24-hour ambulatory blood pressure monitoring (ABPM) (Cohorts 1 and 2 only);
- 12-lead electrocardiograms;
- Clinical laboratory measurements, centrally analyzed;
- Weight.

6.2.3. Exploratory Endpoint(s)

[redacted]



7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This study consists of two parts: a 16-week double-blind, randomized, placebo-controlled treatment period ("Part 1"), followed by an extension period ("Part 2"). All patients who complete treatment in Part 1 may continue to Part 2. Within Part 1, the study consists of a dose-ranging phase and a dose-titration phase. Qualifying patients with PH in both the dose-ranging and dose-titration phases will be followed for safety, tolerability, and efficacy, and all patients enrolled in the study will follow a similar schedule of assessments.

Part 1

Cohorts 1 and 2: In the dose-ranging phase of Part 1 of the study, up to two independently randomized cohorts may be opened at each dose level and patients will be allocated based on their baseline 6MWD (i.e., Cohort 1 for 6MWD ≤ 450 m and Cohort 2 for 6MWD > 450 m). Once opened for enrollment, each dose group will include the next eight eligible patients randomized using a 3:1 assignment ratio (bardoxolone methyl:placebo) to be administered once daily for 16 weeks. Within each cohort type, patients will be enrolled to one dose group at a time.

A Protocol Safety Review Committee (PSRC) will assess the starting dose of 2.5 mg and each new dose level of bardoxolone methyl for safety and tolerability based on review of all available data for this study at the time of each review. PSRC reviews will occur after the Week 4 data are available for the first eight patients enrolled at each new dose level combined across both Cohorts 1 and 2. The PSRC assessment will include a dose level recommendation for subsequent dose groups to escalate to a higher dose, proceed to a lower dose, or maintain the current dose. The PSRC may also recommend stopping dosing for current cohorts. Upon completion of dose ranging, the PSRC will continue to meet at regular intervals (approximately quarterly) to monitor safety of all enrolled patients.

Data from all patients enrolled in Cohort 1 (≤ 450 m patients) and Cohort 2 (> 450 m patients) will be used to provide information regarding the optimal dose range for evaluation of safety, tolerability, and efficacy, allowing the sponsor to select an appropriate dose of bardoxolone methyl for further evaluation in patients with WHO Group I PAH. Selecting from PSRC-recommended dose levels, the sponsor will determine the dose level for each subsequent dose group.

Cohorts 3 and 4: Cohort 3 and Cohort 4 will employ a dose titration scheme intended to identify an optimal dose for each patient. Cohort 3 includes additional WHO Group I patients, while Cohort 4 (PH-ILD cohort) allows only qualified WHO Group III or WHO Group V patients.

Cohort 3 will consist of two subcohorts, randomized independently within each subcohort using a 2:1 assignment ratio (bardoxolone methyl:placebo) to be administered once daily for 16 weeks:

- Cohort 3a will consist of WHO Group I connective tissue disease (CTD)-PAH patients;
- Cohort 3b will consist of WHO Group I non-CTD PAH patients.

Cohort 4 will consist of four subcohorts, randomized independently within each subcohort using a 2:1 assignment ratio (bardoxolone methyl:placebo) to be administered once daily for 16 weeks:

- Cohort 4a will consist of WHO Group III PH patients with connective tissue disease associated interstitial lung disease (CTD-ILD);
- Cohort 4b will consist of WHO Group III PH patients with idiopathic pulmonary fibrosis (IPF);
- Cohort 4c will consist of WHO Group III PH patients with nonspecific interstitial pneumonia (NSIP) or selected idiopathic interstitial pneumonia (IIP) subtypes;
- Cohort 4d will consist of WHO Group V PH patients with sarcoidosis.

Based on the variability in 6MWD change from baseline observed for the first 24 patients enrolled in each subcohort of Cohort 3 and Cohort 4, the Sponsor may choose to increase the number of patients within each subcohort to a maximum of 72 patients. For Cohort 3b, a maximum of approximately 24 patients may be enrolled from the United States.

Patients in Cohorts 3 and 4 will start at 5 mg (or placebo) and will dose escalate to 10 mg at Week 4 unless a dose-limiting toxicity (DLT) is reported (Section 7.3.1). Identification of DLTs is left to the discretion of the Investigator and may include clinically important changes from baseline in BNP, clinical signs of fluid retention, or other adverse events. Suspected DLTs should be discussed with the medical monitor prior to changing dose. If at any time the patient reports an AE that the Investigator considers to be a DLT, the Investigator may choose to decrease the patient's dose to one-half of the prior dose (e.g., 10 mg to 5 mg). Dose de-escalation can occur more than once, but dose reduction is not permitted below a dose of 2.5 mg. Dose escalation during Part 1 is permitted for all patients at Week 4 only.

All patients in Part 1 of the study (i.e., Cohorts 1, 2, 3a-b, and 4a-d) will follow similar visit and assessments schedules. Selected assessments [redacted]) will be optional for all enrolled patients at Sponsor-qualified sites. Other assessments (e.g., ABPM, [redacted]) conducted for Cohorts 1 and 2 will not be conducted for patients in Cohorts 3 and 4. Following randomization, patients will be assessed in person during treatment at Weeks 1, 2, 4, 8, 12, and 16 and by telephone contact on Days 3, 10, and 21. Patients enrolling in Cohorts 3 and 4 will have additional assessments in person at Week 6 and additional telephone contact on Days 31, 38, and 49. Patients who do not enter Part 2 of the study (i.e., the extension period), either because they have discontinued taking study drug during Part 1 or have completed the 16-week treatment period as planned but chosen not to continue to Part 2 of the study, will complete an end-of-treatment visit when patient ends study drug. In addition a follow-up visit should occur four weeks after the date of administration of the last dose of study drug.

Part 2 (extension period):

Patients who discontinue treatment prematurely in study Part 1 are not eligible to continue into study Part 2. All patients from Part 1 who complete the 16-week treatment period as planned will be eligible to continue directly into the extension period to evaluate the intermediate and long-term safety and efficacy of bardoxolone methyl. Day 1 of the extension period will be the same as the Week 16 visit for the treatment period.

Cohort 1 and Cohort 2 patients randomized to placebo in Part 1 of the study will be assigned to receive bardoxolone methyl at their group-specific dose in the extension period. Patients enrolled in Cohorts 1 and 2 may dose titrate to the 10 mg dose or de-escalate at scheduled or unscheduled visits. However, patients who dose escalate must have a telephone call 1 week after

dose escalation and an unscheduled office visit or a home health visit 2 weeks (±3 days) after dose escalation to collect clinical chemistry, BNP, and NT-Pro BNP.

Cohorts 3 and 4 patients randomized to placebo in study Part 1 will be assigned to 5 mg of bardoxolone methyl, whereas, patients randomized to bardoxolone methyl in study Part 1 will begin study Part 2 (Week 16) at the same dose of bardoxolone methyl as they ended with in study Part 1. All patients in Cohorts 3 and 4 will have the option to up-titrate their dose at the Week 20 visit, and may de-escalate in dose (minimum dose of 2.5 mg) at scheduled or unscheduled visits. Treatment assignment will remain blinded for Cohort 3 and 4 patients through Week 20.

Treatment-compliant patients who have completed Part 2 of the study are eligible to continue receiving bardoxolone methyl through an extended access program (Study 402-C-1602). After Week 32, visits will occur every 24 weeks until bardoxolone methyl is available through the extended access program. Once bardoxolone methyl is available through the extended access program, patients in Part 2 who have completed at least 32 weeks of the study will complete an End of Treatment Visit. The Week 32 visit may be the same as the End of Treatment Visit. Beginning with the Week 32 visit, patients will be seen in the clinic every 24 weeks (i.e., Week 56, Week 80, Week 104, etc.) and receive a 6-month supply of study drug at the appropriate dose.

The Sponsor reserves the right to stop the study for a given cohort if development of bardoxolone methyl is discontinued for any reason, or if the assessment of available data raises concerns about the safety or efficacy of bardoxolone methyl.

7.2. Number of Patients

Approximately 198 patients are expected to be enrolled in Part 1 of the study (38 patients in Cohort 1; 16 patients in Cohort 2; and approximately 24 patients in each of Cohorts 3a-b and 4a-d). Based on the variability in 6MWD observed in Cohorts 3 and 4, the Sponsor may choose to increase the number of patients to a maximum of 72 patients in each of Cohorts 3a-b and 4a-d. Variability in 6MWD for each subcohort will be assessed separately. The maximum number of patients enrolled will be 486.

All eligible patients from Part 1 will be included in Part 2, and no new patients will be randomized to Part 2 of the study.

7.3. Treatment Assignment

Patients in Cohorts 1 and 2 will be allocated based on their baseline 6MWD (i.e., Cohort 1 for 6MWD $\leq$ 450 m and Cohort 2 for 6MWD > 450 m). Baseline 6MWD for the purpose of cohort determination is calculated as the average of 2 assessments collected prior to randomization. Patients will be randomized to treatment within each dose group in Part 1 of the study using a 3:1 assignment ratio to receive bardoxolone methyl or matching placebo in Cohorts 1 and 2. Patients in Cohorts 1 and 2 will continue their randomized treatment throughout Part 1 and 2 (i.e., no intra-patient dose escalation). However, upon qualifying for the extension period (Part 2), patients randomized to placebo during the treatment period will begin receiving bardoxolone methyl at their group-specific dose. If the Sponsor decides to continue study Part 2 beyond

12 weeks after the last patient enters the extension part of the study all patients may be assigned or re-randomized to the dose(s) selected for further development.

Cohort 3 and Cohort 4 will employ a dose titration scheme intended to identify an optimal dose for each patient. Cohort 3 includes additional WHO Group I patients, while Cohort 4 (PH-ILD cohort) allows only qualified WHO Group III or WHO Group V patients. Cohort 3 will consist of two subcohorts randomized independently within each subcohort using a 2:1 assignment ratio (bardoxolone methyl:placebo) to be administered once daily for 16 weeks. Cohort 4 will consist of four subcohorts randomized independently within each subcohort using a 2:1 assignment ratio (bardoxolone methyl:placebo) to be administered once daily for 16 weeks.

Patients in Cohorts 3 and 4 will start at 5 mg (or placebo) and will dose escalate to 10 mg at Week 4 unless a dose-limiting toxicity (DLT) is reported (Section 7.3.1). If at any time the patient reports an AE that the Investigator considers to be a DLT, the Investigator may choose to decrease the patient's dose to one-half of the prior dose (e.g., 10 mg to 5 mg). The minimum allowed dose is 2.5 mg. Dose escalation during Part 1 is permitted for all patients at Week 4 only.

Cohort 3 and 4 patients randomized to placebo in study Part 1 will be assigned to 5 mg of bardoxolone methyl, whereas, patients randomized to bardoxolone methyl in study Part 1 will begin study Part 2 (Week 16) at the same dose of bardoxolone methyl as they ended with in study Part 1. All patients in Cohorts 3 and 4 will have the option to up-titrate their dose at the Week 20 visit, and may de-escalate in dose at scheduled or unscheduled visits. Treatment assignment will remain blinded for Cohort 3 and 4 patients through Week 20. Dose escalation during the extension period is permitted for all patients at the Week 20 visit only.

7.3.1. Criteria for Determining Dose-Limiting Toxicity

The assessment of a DLT (i.e., a side effect serious enough to prevent an increase in dose or to warrant a decrease in dose) will be based on the clinical judgment of the Investigator, and may include clinically important changes from baseline in BNP, clinical signs of fluid retention, and/or serious adverse events associated with study drug administration. Suspected DLTs should be discussed with the medical monitor before dose de-escalation.

7.4. Criteria for Study Termination

Although the Sponsor intends to complete the study, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons, or if required by regulatory agencies. If the Sponsor discontinues the study, all study treatment will be discontinued and the Investigator will be responsible for securing any alternative therapy to be administered, as appropriate.

7.5. Schedule of Assessments

Table 3, Table 4, Table 5, and Table 6 list the overall schedule of assessments for the study.

Table 3: Part 1: Schedule of Assessments for Patients in Cohorts 1 and 2

Assessment / Study Week (Day)	Screen A[a]	Screen B[a]	Day 1[b]	Week 1 (Phone) Day 3±1	Week 1[c] Day 7±3	Week 2 (Phone) Day 10±1	Week 2[c] Day 14±3	Week 3 (Phone) Day 21±3	Week 4 Day 28±3	Week 8 Day 56±3	Week 12 Day 84±3	Week 16 or End of Treatment Visit[d] Day 112±3	Follow-up[d]
Informed consent	X												
Inclusion/ exclusion	X		X[e]										
Demographics and baseline disease characteristics	X												
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X
Medical history	X												
Height	X												
Weight in clinic	X		X		X		X		X	X	X	X	X
Weight at home			X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	
Dispense weight diary			X		X		X		X	X	X	X	
Collect/review weight diary				X	X	X	X	X	X	X	X	X	
ECG	X											X	X
Vital sign measurements	X		X		X		X		X	X	X	X	X
Physical exam[g]/clinical worsening assessment[h]	X		X		X[i]		X[i]		X	X	X	X	X
Pregnancy test for WOCBP[j]	X		X									X	X
Study drug administration			X	---------- X ----------									
Dispense study drug			X						X	X	X		
Collect study drug									X	X	X	X	
Telephone contact				X		X		X					
Adverse event collection			X[k]	X	X	X	X	X	X	X	X	X	X
Clinical chemistry	X		X		X		X		X	X	X	X	X
BNP and NT-Pro BNP[l]	X		X		X		X		X	X	X	X	X
Hematology	X		X		X		X		X	X	X	X	X
Urinalysis and microscopy	X		X		X		X		X	X	X	X	X
Virus serology[m]	X												
6-min walk test	X[n]	X[n]							X[n]	X	X	X[n]	X
ECHO[o]	X[p]		X						X			X	
[redacted]													
[redacted]													
[redacted]													
[redacted]													

Assessment \ Study Week (Day)	Screen A[a]	Screen B[a]	Day 1[b]	Week 1 (Phone) Day 3±1	Week 1[c] Day 7±3	Week 2 (Phone) Day 10±1	Week 2[c] Day 14±3	Week 3 (Phone) Day 21±3	Week 4 Day 28±3	Week 8 Day 56±3	Week 12 Day 84±3	Week 16 or End of Treatment Visit[d] Day 112±3	Follow-up[d]
24-hour ambulatory blood pressure monitoring (ABPM)		X[s]							X			X	
Pulmonary function testing/ Right Heart Catheterization	X[t]												
[redacted]													
[redacted]													
Functional class assessment[w]	X		X									X	X
PK samples[x]									X				

[a] Total screening period should not exceed 28 days.

[b] Study Day 1 is the day of administration of the first dose. **On Study Day 1, all procedures should be performed before study drug administration.**

[c] Under the delegation of the Investigator and following Sponsor prior approval for each visit, a patient may be seen by a home health professional, qualified by documented training to perform study-specific procedures.

[d] Patients who discontinue from the study prior to the Week 16 study visit will need to be brought back for all early termination assessments (i.e., both an end-of-treatment visit and then a follow-up visit 4 weeks after the date of administration of the last dose of study drug). Patients should complete the end-of-treatment procedures, including the 6MWT, prior to any adjustments being made to their PAH treatment regimen.

[e] Screen A and Screen B eligibility procedures do not need to be repeated on Day 1; however, a review of any changes in eligibility criteria should be evaluated prior to Day 1 procedures, and a urine pregnancy test should be performed for WOCBP.

[f] Weights taken at home by the patient will begin on Day 2 and should be taken daily for the first 4 weeks and weekly thereafter, preferably at the same time each day and must be recorded in a diary and reviewed with the coordinator during telephone contacts and office visits.

[g] Physical examinations must be performed by a qualified physician, physician's assistant, or registered nurse practitioner.

[h] If clinical worsening is suspected, further clinical evaluations may be required per Section 9.10.32.

[i] If the visit is completed by home health professional, a limited physical assessment directed to assess for fluid retention and clinical worsening will be performed under the delegation of the Investigator

[j] A serum pregnancy test will be performed at Screen A for WOCBP or at any point in time if a pregnancy is suspected. All other pregnancy assessments will be urine pregnancy tests. Additional pregnancy assessments will be performed more frequently if required by local law or requested by local regulatory authorities or IRBs/ECs.

[k] AE assessments on Day 1 should be done following study drug administration.

[l] Patients must be allowed to rest for a minimum period of one hour following arrival at the clinic and prior to collecting this blood sample. Similarly, this sample must be taken prior to the 6MWT. This sample should be taken with the patient in the same position at all appropriate visits, e.g., sitting or semi-recumbent.

[m] Tests for hepatitis B and hepatitis C. If the initial hepatitis C result is positive, then the patient will need to return for an unscheduled HCV RNA assessment to determine if the virus is present at the current time. If the results of this test are negative, the patient may continue in the screening process.

[n] The 6-minute walk test must be performed on two separate days prior to randomization and on 2 separate days within the Week 4 and Week 16 3-day window.

[o] Day 1 ECHO, [redacted] can be performed anytime after the patient qualifies (completed Screen A and Screen B) for the study and prior to study drug administration. The Week 4 and 16 ECHO, [redacted] assessments must occur within the visit window (+/- 3 days); however, they can be performed on different days than the other visit assessments. [redacted]

[p] Echocardiography (ECHO) within 60 days prior to Day 1 may be used to determine eligibility

[q] [redacted]

[s] Prior to randomization, the patient must have a qualified 24-hour ABPM assessment. If first 24-hour assessment is not qualified, one re-test may be performed prior to randomization. If the second test result does not qualify the patient will be considered a screen failure.
[t] Pulmonary function tests within 90 days prior to Day 1 may be used to determine eligibility. Right heart catheterization within 36 months prior to Day 1 may be used to determine eligibility.
[u] Completed immediately following the completion of the 6MWT.
[v] [redacted]
[w] If clinical worsening is suspected, perform unscheduled functional class assessment.
[x] Blood samples for PK analysis should be drawn just prior to (0 hour) and after (2 and 4 hours) dose administration for this visit. Patients should be instructed to not take their study drug prior to coming to the clinic at Week 4.

Abbreviations: ECG = electrocardiogram, ECHO = echocardiogram, PK = pharmacokinetic, s = serum, u = urine, WOCBP = women of child-bearing potential, [redacted] 6MWT = 6-minute walk test

Table 4: Part 1: Schedule of Assessments for Patients in Cohort 3 and Cohort 4 (PH-ILD Cohort)

Study Week (Day) / Assessment	Screen A[a]	Day 1[b]	Week 1 (Phone) Day 3±1	Week 1[c] Day 7±3	Week 2 (Phone) Day 10±1	Week 2[c] Day 14±3	Week 3 (Phone) Day 21±3	Week 4 Day 28±3	Week 4 (Phone) Day 31±3	Week 5 (Phone) Day 38±3	Week 6[c] Day 42±3	Week 7 (Phone) Day 49±3	Week 8 Day 56±3	Week 12 Day 84±3	Week 16 or End of Treatment Visit[d] Day 112±3	F/U[d]
Informed consent	X															
Inclusion/ exclusion	X	X[e]														
Demographics and baseline disease characteristics	X															
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical history	X															
Height	X															
Weight in clinic	X	X		X		X		X			X		X	X	X	X
Weight at home[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense weight diary		X		X		X		X			X		X	X		
Collect/review weight diary			X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG	X														X	X
Vital sign measurements	X	X		X		X		X			X		X	X	X	X
Physical exam/clinical worsening assessment[g]	X	X		X		X		X			X		X	X	X	X
Pregnancy test for WOCBP[h]	X	X													X	X
Study drug administration		X	---------- X ----------													
Dispense study drug		X						X					X	X		
Collect study drug								X					X	X	X	
Telephone contact			X		X		X		X	X		X				
Adverse event collection		X[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical chemistry	X	X		X		X		X			X		X	X	X	X
BNP and NT-Pro BNP[j]	X	X		X		X		X			X		X	X	X	X
Hematology	X	X		X		X		X			X		X	X	X	X
Urinalysis and microscopy	X	X		X		X		X			X		X	X	X	X
Virus serology[k]	X															
6-min walk test	X	X[l]						X					X	X	X[m]	X
ECHO	X[n]															
[redacted]																
Pulmonary function testing[r]	X	X						X					X	X	X	X

Study Week (Day) / Assessment	Screen A[a]	Day 1[b]	Week 1 (Phone) Day 3±1	Week 1[c] Day 7±3	Week 2 (Phone) Day 10±1	Week 2[c] Day 14±3	Week 3 (Phone) Day 21±3	Week 4 Day 28±3	Week 4 (Phone) Day 31±3	Week 5 (Phone) Day 38±3	Week 6[c] Day 42±3	Week 7 (Phone) Day 49±3	Week 8 Day 56±3	Week 12 Day 84±3	Week 16 or End of Treatment Visit[d] Day 112±3	F/U[d]
[redacted]	[redacted]	[redacted]						[redacted]					[redacted]	[redacted]	[redacted]	[redacted]
Right Heart Catheterization	X															
[redacted]	[redacted]	[redacted]						[redacted]					[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]													[redacted]	
[redacted]	[redacted]	[redacted]													[redacted]	[redacted]
PK samples[v]								X								
[redacted]	[redacted]														[redacted]	
[redacted]	[redacted]														[redacted]	
[redacted]	[redacted]															
Below assessments for Cohort 4d only[z]																
[redacted]	[redacted]														[redacted]	
	[redacted]														[redacted]	
	[redacted]														[redacted]	
	[redacted]														[redacted]	
	[redacted]														[redacted]	

[a] Total screening period should not exceed 60 days. If screening is longer than 28 days, BNP should be repeated through the central lab prior to randomization.

[b] Study Day 1 is the day of administration of the first dose. **On Study Day 1, all procedures should be performed before study drug administration.**

[c] Under the delegation of the Investigator and following Sponsor prior approval for each visit, a patient may be seen by a home health professional, qualified by documented training to perform study-specific procedures. If the visit is completed by home health professional, a limited physical assessment directed to assess for fluid retention and clinical worsening will be performed under the delegation of the Investigator

[d] Patients who discontinue from the study prior to the Week 16 study visit will need to be brought back for all early termination assessments (i.e., both an end-of-treatment visit and then a follow-up visit 4 weeks after the date of administration of the last dose of study drug). Patients should complete the end-of-treatment procedures, including the 6MWT, prior to any adjustments being made to their PAH treatment regimen.

[e] Screen A eligibility procedures do not need to be repeated on Day 1; however, a review of any changes in eligibility criteria should be evaluated prior to Day 1 procedures, and a urine pregnancy test should be performed for WOCBP.

[f] Weights taken at home by the patient will begin on Day 2 and should be taken daily for the first 8 weeks and weekly thereafter, preferably at the same time each day and must be recorded in a diary and reviewed with the coordinator during telephone contacts and office visits.
[g] If clinical worsening is suspected, further clinical evaluations may be required per Section 9.10.32.
[h] A serum pregnancy test will be performed at Screen A for WOCBP or at any point in time if a pregnancy is suspected. All other pregnancy assessments will be urine pregnancy tests. Additional pregnancy assessments will be performed more frequently if required by local law or requested by local regulatory authorities or IRBs/ECs.
[i] AE assessments on Day 1 should be done following study drug administration.
[j] Patients must be allowed to rest for a minimum period of one hour following arrival at the clinic and prior to collecting this blood sample. Similarly, this sample must be taken prior to the 6MWT. This sample should be taken with the patient in the same position at all appropriate visits, e.g., sitting or semi-recumbent.
[k] Tests for hepatitis B and hepatitis C. If the initial hepatitis C result is positive, then the patient will need to return for an unscheduled HCV RNA assessment to determine if the virus is present at the current time. If the results of this test are negative, the patient may continue in the screening process.
[l] The 6-minute walk test on Day 1 is used to confirm eligibility and must be performed prior to randomization.
[m] The 6-minute walk test must be performed on 2 separate days within the Week 16 3-day window.
[n] Echocardiography (ECHO) within 60 days prior to Day 1 may be used to determine eligibility
[redacted]
[r] All patients must have PFTs assessed within 90 days prior to Day 1 to determine eligibility.
[redacted]
[u] If clinical worsening is suspected, perform unscheduled functional class assessment.
[v] Blood samples for PK analysis should be drawn just prior to (0 hour) and after (2 and 4 hours) dose administration for this visit. Patients should be instructed to not take their study drug prior to coming to the clinic at Week 4.
[redacted]

Abbreviations: ECG = electrocardiogram, PK = pharmacokinetic, s = serum, u = urine, WOCBP = women of child-bearing potential, [redacted] 6MWT = 6-minute walk test, F/U = Follow-up

Table 5: Part 2: Extension Schedule of Assessments for Patients in Cohorts 1 and 2

Assessment \ Study Week	Week 16[a] (Day 1) (±3 days)	Week 17 (Phone) (±1 day)	Week 18[b] (±3 days)	Week 19 (Phone) (±1 day)	Week 20 (±3 days)	Week 32 (± 5 days)	Week 56 and Every 24 Weeks Thereafter (±5 days)[c]	End of Treatment Visit[d] (± 5 days)	Follow-up[d] (± 5 days)
Concomitant medications		X	X	X	X	X	X	X	X
Weight in clinic			X		X	X	X	X	X
Weight at home[e]		X	X	X	X	X	X		
Dispense weight diary	X		X		X	X	X		
Collect/Review weight diary		X	X	X	X	X	X	X	
ECG						X		X	X
Vital sign measurements			X		X	X	X	X	X
Physical exam/clinical worsening assessment[f]			X[g]		X	X	X	X	X
Urine Pregnancy test for WOCBP[h]						X	X	X	X
Study drug administration	X	---------- X ----------							
Dispense study drug	X				X	X	X		
Collect study drug					X	X	X	X	
Telephone contact[i]		X		X					
Adverse event collection		X	X	X	X	X	X	X	X
Clinical chemistry[j]			X		X	X	X	X	X
BNP and NT-Pro BNP[j,k]			X		X	X	X[k]	X[k]	X
Hematology			X		X	X	X	X	X
Urinalysis and microscopy			X		X	X	X	X	X
6-min walk test					X	X	X	X	X
[redacted]					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						[redacted]		[redacted]	
Functional class assessment[m]						X		X	X
PK samples[n]					X				

[a] All other Week 16 assessments will be completed as per Table 3 or Table 4.

[b] Under delegation of the Investigator and with prior Sponsor approval, a patient may be seen by a home health professional. The home health professional must have documented study-specific training on file prior to the performance of any study-related procedures.

[c] Visits beyond Week 32 will only occur until bardoxolone methyl is available through the extended access program. Once bardoxolone methyl is available through the extended access program, patients in Part 2 who have completed at least 32 weeks of the study will complete an End of Treatment Visit. If bardoxolone methyl is available through the extended access program prior to Week 32, the End of Treatment visit may coincide with the Week 32 visit.

[d] Patients who are discontinued from the study during the extension period for any reason, including Sponsor termination of the study, and patients who are not participating in the extended access program must complete all end-of-treatment and follow-up visit assessments. Patients should complete the end-of-treatment assessments, including the 6MWT, prior to any adjustments being made to their PAH-specific treatment regimen.

[e] Weights taken at home by the patient should be taken daily starting at week 16 through and including week 20 and weekly thereafter, preferably at the same time each day and must be recorded in a diary and reviewed with the coordinator during telephone contacts and office visits.
[f] If clinical worsening is suspected, further clinical evaluations may be required per Section 9.10.32.
[g] A limited physical assessment directed to assess for fluid retention and clinical worsening may be performed by a home health professional under the delegation of the Investigator
[h] A serum pregnancy test will be performed at Screen A for WOCBP or at any point in time if a pregnancy is suspected. All other pregnancy assessments will be urine pregnancy tests. Additional pregnancy assessments will be performed more frequently if required by local law or requested by local regulatory authorities or IRBs/ECs.
[i] Patients who dose escalate must be have a telephone call 1 week after dose escalation and an unscheduled office visit or home health 2 weeks (± 3 days) after dose escalation to collect clinical chemistry, BNP and NT-Pro BNP, as well as a telephone call.
[j] Patients must be allowed to rest for a minimum period of one hour following arrival at the clinic and prior to obtaining this blood sample. Similarly, this sample must be taken prior to the 6MWT. This sample should be taken with the patient in the same position at all appropriate visits, e.g., sitting or semi-recumbent.
[k] After Week 32, only NT-Pro BNP will be collected.
[l] [redacted]
[m] If clinical worsening is suspected, perform unscheduled functional class assessment.
[n] Blood samples for PK analysis should be drawn just prior to (0 hour) and after (2 and 4 hours) dose administration for this visit. Patients should be instructed to not take their study drug prior to coming to the clinic at Week 20.

Abbreviations: ECG = electrocardiogram, ECHO = echocardiogram, PK = pharmacokinetic, s = serum, u = urine, WOCBP = women of child-bearing potential, [redacted]

Table 6: Part 2: Extension Schedule of Assessments for Patients in Cohorts 3 and 4

Assessment \ Study Week	Week 16[a] (Day 1) (±3 days)	Week 17 (Phone) (±1 day)	Week 18[b] (±3 days)	Week 19 (Phone) (±1 day)	Week 20 (±3 days)	Week 21 (Phone) (±1 day)	Week 22[b] (±3 days)	Week 23 (Phone) (±1 day)	Week 24[b] (±3 days)	Week 32 (± 5 days)	Week 56 and Every 24 Weeks Thereafter (±5 days)[c]	End of Treatment Visit[d] (± 5 days)	Follow-up[d] (± 5 days)
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X
Weight in clinic			X		X		X		X	X	X	X	X
Weight at home[e]		X	X	X	X	X	X	X	X	X	X		
Dispense weight diary	X		X		X		X		X	X	X		
Collect/Review weight diary		X	X	X	X	X	X	X	X	X	X	X	
ECG										X		X	X
Vital sign measurements			X		X		X		X	X	X	X	X
Physical exam/clinical worsening assessment[f]			X[g]		X		X[g]		X[g]	X	X	X	X
Urine Pregnancy test for WOCBP[h]										X	X	X	X
Study drug administration	X	---------- X ----------											
Dispense study drug	X				X					X	X		
Collect study drug					X					X	X	X	
Telephone contact		X		X		X		X					
Adverse event collection		X	X	X	X	X	X	X	X	X	X	X	X
Clinical chemistry			X		X		X		X	X	X	X	X
BNP and NT-Pro BNP[i,j]			X		X		X		X	X	X[h]	X[i]	X
Hematology			X		X		X		X	X	X	X	X
Urinalysis and microscopy			X		X		X		X	X	X	X	X
6-min walk test					X					X	X	X	X
[redacted]					[redacted]					[redacted]	[redacted]	[redacted]	[redacted]
[redacted]										[redacted]		[redacted]	
Functional class assessment[l]										X		X	X
PK samples[m]					X								
Pulmonary Function Testing	X				X					X		X	X
[redacted]	[redacted]				[redacted]					[redacted]		[redacted]	[redacted]

[a] All other Week 16 assessments will be completed as per Table 3 or Table 4.

[b] Under delegation of the Investigator and with prior Sponsor approval, a patient may be seen by a home health professional. The home health professional must have documented study-specific training on file prior to the performance of any study-related procedures.

[c] Visits beyond Week 32 will only occur until bardoxolone methyl is available through the extended access program. Once bardoxolone methyl is available through the extended access program, patients in Part 2 who have completed at least 32 weeks of the study will complete an End of Treatment Visit. If bardoxolone methyl is available through the extended access program prior to Week 32, the End of Treatment visit may coincide with the Week 32 visit.

[d] Patients who are discontinued from the study during the extension period for any reason, including Sponsor termination of the study, and patients who are not participating in the extended access program must complete all end-of-treatment and follow-up visit assessments. Patients should complete the end-of-treatment assessments, including the 6MWT, prior to any adjustments being made to their PAH-specific treatment regimen.

[e] Weights taken at home by the patient should be taken daily starting at week 16 through and including week 20 and weekly thereafter, preferably at the same time each day and must be recorded in a diary and reviewed with the coordinator during telephone contacts and office visits.
[f] If clinical worsening is suspected, further clinical evaluations may be required per Section 9.10.32.
[g] A limited physical assessment directed to assess for fluid retention and clinical worsening may be performed by a home health professional under the delegation of the Investigator and with prior Sponsor approval.
[h] A serum pregnancy test will be performed at Screen A for WOCBP or at any point in time if a pregnancy is suspected. All other pregnancy assessments will be urine pregnancy tests. Additional pregnancy assessments will be performed more frequently if required by local law or requested by local regulatory authorities or IRBs/ECs.
[i] Patients must be allowed to rest for a minimum period of one hour following arrival at the clinic and prior to obtaining this blood sample. Similarly, this sample must be taken prior to the 6MWT. This sample should be taken with the patient in the same position at all appropriate visits, e.g., sitting or semi-recumbent.
[j] After Week 32, only NT-Pro BNP will be collected.
[redacted]
[l] If clinical worsening is suspected, perform unscheduled functional class assessment.
[m] Blood samples for PK analysis should be drawn just prior to (0 hour) and after (2 and 4 hours) dose administration for this visit. Patients should be instructed to not take their study drug prior to coming to the clinic at Week 20.
[redacted]

Abbreviations: ECG = electrocardiogram, ECHO = echocardiogram, PK = pharmacokinetic, s = serum, u = urine, WOCBP = women of child-bearing potential, [redacted]

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Patient Inclusion Criteria

Diagnosis and main criteria for inclusion:

1. Adult male and female patients ≥ 18 to ≤ 75 years of age upon study consent;
2. BMI > 18.5 kg/m^2;
3. Symptomatic pulmonary hypertension WHO Functional Class II and III;
4. WHO Group I, III, or V PH according to the following criteria:
    a. If diagnosed with WHO Group I PAH, then one of the following subtypes:
        i. Idiopathic or heritable PAH;
        ii. PAH associated with connective tissue disease;
        iii. PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following shunt repair;
        iv. PAH associated with anorexigen or drug-induced toxicity;
        v. PAH associated with human immunodeficiency virus (HIV); or
    b. If WHO Group III PH, then primary diagnosis must be one of the following subtypes:
        i. Connective tissue disease associated ILD (CTD-ILD);
        ii. Idiopathic pulmonary fibrosis (IPF), according to the American Thoracic Society and European Respiratory Society (ATS/ERS) guidelines (Raghu 2011);
        iii. Nonspecific interstitial pneumonia (NSIP) or the following idiopathic interstitial pneumonia subtypes, according to the American Thoracic Society and European Respiratory Society (ATS/ERS) guidelines (Travis 2013):
            1. Respiratory bronchiolitis-associated interstitial lung disease;
            2. Desquamative interstitial pneumonia;
            3. Cryptogenic organizing pneumonia;
            4. Acute interstitial pneumonitis;
            5. Idiopathic lymphoid interstitial pneumonia;
            6. Idiopathic pleuroparenchymal fibroelastosis;
            7. Unclassifiable idiopathic interstitial pneumonia, including patients who have not had a lung biopsy; or
    c. If WHO Group V PH, then patient must be diagnosed with sarcoidosis;

5. Had a diagnostic right heart catheterization performed and documented prior to Day 1 that confirmed a diagnosis of PH according to all the following criteria:
    a. If diagnosed with WHO Group I PAH, then:
        i. Mean pulmonary artery pressure ≥ 25 mm Hg (at rest);
        ii. Pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg;
        iii. Pulmonary vascular resistance > 240 dyn.sec/cm^5 or > 3 mm Hg/Liter (L)/minute;
    b. If not diagnosed with WHO Group I PAH, then:
        i. Mean pulmonary artery pressure ≥ 21 mm Hg (at rest);
        ii. Pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg;
        iii. Pulmonary vascular resistance > 160 dyn.sec/cm^5;
6. Has BNP level ≤ 400 pg/mL;
7. Has an average 6-minute walk distance (6MWDs) ≥ 150 meters on two consecutive tests performed on different days prior to randomization, with both tests measuring within 15% of one another;
8. Has been receiving no more than two (2) approved disease-specific PAH therapies. Cohort 3b WHO Group I PAH patients enrolled outside the United States must be receiving zero (0) or one (1) PAH therapies. PAH therapy must be at a stable dose for at least 90 days prior to Day 1;
9. If WHO Group III or WHO Group V, disease-specific therapy must be at a stable dose for 30 days;
10. Has maintained a stable dose for 30 days prior to Day 1 if receiving any of the following therapies that may affect PH: vasodilators (including calcium channel blockers), digoxin, L-arginine supplementation, or oxygen supplementation;
11. If receiving prednisone, has maintained a stable dose of ≤ 20 mg/day (or equivalent dose if other corticosteroid) for at least 30 days prior to Day 1. If receiving treatment for connective tissue disease (CTD) with any other drugs, doses should remain stable for the duration of the study;
12. Had pulmonary function tests (PFTs) within 90 days prior to Day 1 that meet the following criteria:
    a. For WHO Group I PAH patients with connective tissue disease, total lung capacity (TLC) ≥ 65% (predicted);
    b. For all other WHO Group I PAH patients,
        i. Forced expiratory volume in 1 second (FEV1) ≥ 65% (predicted); or
        ii. FEV1/forced vital capacity ratio (FEV1/FVC) ≥ 65%;
    c. For WHO Group III or V PH patients, total lung capacity (TLC) between 50-90% (predicted);

13. For WHO Group I patients, had a ventilation-perfusion (V/Q) lung scan or spiral/helical/electron beam computed tomography (CT) or pulmonary angiogram prior to Screening that shows no evidence of thromboembolic disease (i.e., should note normal or low probability for pulmonary embolism). If V/Q scan was abnormal (i.e., results other than normal or low probability), then a confirmatory CT or selective pulmonary angiography must exclude chronic thromboembolic disease;
14. Has adequate kidney function defined as an estimated glomerular filtration rate (eGFR) $\geq$ 45 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) 4-variable formula;
15. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures;
16. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study prior to initiation of any patient-mandated procedures;
17. For WHO Group III or V PH patients, the presence of ILD must be confirmed by a diagnostic high resolution computed tomography (HRCT) scan or biopsy performed and documented prior to Day 1.

8.2. Patient Exclusion Criteria

All patients with any of the following conditions or characteristics must be excluded from the study:

1. Participation in other investigational clinical studies involving pharmaceutical products being tested or used in a way different from the approved form or when used for an unapproved indication within 30 days of Day 1;
2. Initiation of an exercise program for cardio-pulmonary rehabilitation within 3 months (90 days) prior to Day 1 or planned initiation during Part 1 of the study;
3. Stopped receiving any PH chronic therapy within 60 days prior to Day 1;
4. Requirement for receipt of intravenous inotropes within 30 days prior to Day 1;
5. Has uncontrolled systemic hypertension as evidenced by sitting systolic blood pressure (BP) > 160 mm Hg or sitting diastolic blood pressure > 100 mm Hg during Screening after a period of rest;
6. Has systolic BP < 90 mm Hg during Screening after a period of rest;
7. WHO Group III patients with pulmonary hypertension primarily associated with chronic obstructive pulmonary disease, sleep-disordered breathing, and/or alveolar hypoventilation disorders;
8. WHO Group III or V patients who at rest require supplemental oxygen at a rate > 4 L/min or have peripheral capillary oxygen saturation (SpO2) levels <92%;

9. Has a history of clinically significant left-sided heart disease and/or clinically significant cardiac disease, including but not limited to any of the following:
    a. Congenital or acquired valvular disease if clinically significant apart from tricuspid valvular insufficiency due to pulmonary hypertension;
    b. Pericardial constriction;
    c. Restrictive or congestive cardiomyopathy;
    d. Left ventricular ejection fraction < 40% per echocardiogram (ECHO) within 60 days of Day 1;
    e. Any current or prior history of symptomatic coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or anginal chest pain);
10. Clinical instability within 8 weeks prior to Day 1, such as hospitalization due to respiratory or cardiac symptoms, acutely decompensated heart failure, syncope, or other events that in the investigator's opinion would suggest the patient is an inappropriate candidate for the study;
11. Has more than two of the following clinical risk factors for left ventricular diastolic dysfunction:
    a. Age > 65 years;
    b. BMI ≥ 30 kg/m^2;
    c. History of systemic hypertension;
    d. History of type 2 diabetes;
    e. History of atrial fibrillation;
12. History of atrial septostomy within 180 days prior to Day 1;
13. Obstructive sleep apnea that is untreated;
14. For patients with HIV-associated PAH, any of the following:
    a. Concomitant active opportunistic infections within 180 days prior to Screening;
    b. Detectable viral load within 90 days prior to Screening;
    c. Cluster designation 4 (CD4+) T-cell count < 200 mm^3 within 90 days prior to Screening;
    d. Changes in antiretroviral regimen within 90 days prior to Screening;
    e. Using inhaled pentamidine;
15. Has a history of portal hypertension or chronic liver disease, including hepatitis B and/or hepatitis C (with evidence of recent infection and/or active virus replication) defined as mild to severe hepatic impairment (Child-Pugh Class A-C);
16. Serum aminotransferase (ALT or AST) levels > 1.5X the upper limit of normal (ULN) at Screening;

17. Hemoglobin (Hgb) concentration < 10.5 g/dL at Screening;
18. Diagnosis of Down syndrome;
19. History of malignancy within 5 years prior to screening, with the exception of localized skin or cervical carcinomas;
20. Active bacterial, fungal, or viral infection, incompatible with the study;
21. Known or suspected active drug or alcohol abuse, per Investigator judgment;
22. Major surgery within 30 days prior to Screening or planned to occur during the course of the study;
23. Unwilling to practice methods of birth control (both males who have partners of childbearing potential and females of childbearing potential) during screening, while taking study drug and for at least 30 days after the last dose of study drug is ingested;
24. Women who are pregnant or breastfeeding;
25. Any disability or impairment that would prohibit performance of the 6MWT;
26. Any abnormal laboratory level that, in the opinion of the Investigator, would put the patient at risk by trial enrollment;
27. Patient is, in the opinion of the Investigator, unable to comply with the requirements of the study protocol or is unsuitable for the study for any reason;
28. Known hypersensitivity to any component of the study drug;
29. Unable to communicate or cooperate with the Investigator due to language problems, poor mental development, or impaired cerebral function;
30. Use of intravenous (iv) or subcutaneous (sc) prostacyclin/prostacyclin analogues;
31. Prior exposure to bardoxolone methyl.

8.3. Patient Re-screening

Patients may repeat the screening procedures to qualify for the study with approval from the medical monitor.

8.4. Patient Withdrawal and Discontinuation

Patients have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The Investigator may discontinue a patient from the study for any of the following reasons:

- Clinical worsening;
- Occurrence of an adverse event or change in medical status that leads the Investigator or Sponsor to be concerned about the patient's welfare;
- Investigator determines the patient is non-compliant with study procedures;
- Females who become pregnant during the study;
- Failure to return for follow-up.

Patients must be withdrawn from the study if any of the following occur.

- ALT or AST > 8X ULN;
- ALT or AST > 5X ULN for 14 days;
- ALT or AST > 3X ULN and (total bilirubin > 2X ULN or INR > 1.5);
- ALT or AST > 3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%);
- Withdrawal of consent;
- Death.

Patients who discontinue from the study will be asked to complete the end-of treatment and follow-up procedures noted in Table 3 or Table 4 and Table 5 or Table 6 depending on which cohort the patient is enrolled in and whether the patient is Part 1 or 2 of the study. Patients who complete the 16 weeks of Part 1 but choose not to participate in Part 2 (the extension period) should complete the follow-up procedures in Table 3 or Table 4 and Table 5 or Table 6. Patients should complete end-of-treatment procedures, including the 6MWT, prior to any adjustments being made to their PAH treatment regimen. Patients who discontinue for elevated transaminase levels should complete the End-of-treatment visit, the Follow-up visit **and** should also be followed per Section 9.1.2 if acceptable levels are not reached at the Follow-up visit.

Every effort should be made to contact patients who do not return for a scheduled visit. The Investigator should inquire about the reason for withdrawal, request the patient return all unused investigational product(s), request the patient return for end-of-treatment and follow-up visits (if applicable), and follow-up with the patient regarding any unresolved AEs. Patients who discontinue participating in the study for any reason may not re-enter the study at any time.

9. TREATMENT OF PATIENTS

9.1. Select Management Guidelines

The following guidelines apply to the management of study participants:

9.1.1. Management of Fluid Status

Specific risk mitigation procedures will be employed to reduce the potential for bardoxolone methyl-induced fluid overload. These procedures include exclusion of patients with any clinically significant renal disease, defined as an eGFR value of < 45 mL/min/1.73 m^2. To exclude patients with significant cardiac dysfunction, the study will exclude patients with a history of left-sided heart disease. Patients who have evidence of volume overload at baseline, defined as BNP level of > 400 pg/mL, will also be excluded. Laboratory data will also be used to monitor fluid status after randomization.

Additionally, after randomization patients will be closely monitored for rapid weight gain suggestive of fluid overload. Patients will be given a Sponsor-provided scale to use at home to collect and record their weights daily during the first 4 weeks (Cohorts 1 and 2) or 8 weeks (Cohorts 3 and 4) of the treatment period and weekly thereafter. Patients who experience a five-pound (2.3 kilogram) or greater increase in weight since their Day 1 weight during Part 1 and during the first 4 weeks (Cohorts 1 and 2) or 8 weeks (Cohorts 3 and 4) of Part 2 will be instructed to stop taking their study medication immediately and return to the clinic for an unscheduled physical examination and laboratory assessment by the Investigator. Patients may not restart their study medication until the Investigator has completed and documented an assessment of fluid overload.

Investigators should also advise patients to watch for signs and symptoms of fluid overload. Patients should be informed to notify their physicians immediately if they experience swollen feet, chest pain, and shortness of breath with mild exertion or while lying down, or other relevant symptoms. The Investigator should immediately assess symptoms of fluid overload and determine appropriate medical management, as necessary, including whether stopping drug administration is required. At the earliest sign of worsening or new onset peripheral edema or other signs and symptoms of acute volume overload, Investigators will also be expected to determine if changes to a patient's diuretic regimen is needed.

Since placebo patients will be transitioned to active treatment for the extension period (Part 2), and the blind will be maintained, all patients entering the extension will be closely monitored for weight gain just as they were monitored following randomization into the treatment period. Patients will use their Sponsor-provided scale during the first four weeks (Cohorts 1 and 2) or eight weeks (Cohorts 3 and 4) of the extension period and will record their weights daily. As in the treatment period (Part 1), patients will be instructed to stop taking their study medication immediately and return to the clinic for an unscheduled physical examination and laboratory assessment by the Investigator if they experience a five-pound or greater increase in weight since Week 16 (Day 1 of the extension period).

9.1.2. Management of Elevated Transaminase Levels (ALT and/or AST)

Nearly all instances of elevated transaminases are expected to be asymptomatic. Check transaminase levels (as well as total bilirubin (TBL), GGT, alkaline phosphatase (ALP), and International Normalized Ratio (INR) within 48-72 hours during an unscheduled visit if the following occurs:

- ALT or AST levels > 3X ULN

Repeat testing every 72 to 96 hours until transaminase levels are below three times the ULN for at least one week or the patient withdraws consent.

Discontinue study drug administration permanently if any of the following occurs:

- ALT or AST > 8X ULN
- ALT or AST > 5X ULN for more than 2 weeks
- ALT or AST > 3X ULN and [TBL > 2 x ULN **or** INR > 1.5]
- ALT or AST > 3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%); The hepatobiliary tree must be visualized (e.g., ultrasound, MRI) and assessed if a patient discontinues taking study drug secondary to elevated transaminase levels. Additional tests/studies may be warranted depending on the clinical presentation.

9.1.3. Management of Muscle Spasms

Basic symptomatic relief is the first step in managing muscle spasm, including walking, adequate hydration, wearing socks, and stretching before bedtime. Assessment of levels of electrolytes such as magnesium, calcium and potassium may indicate the need for replacement. If vitamin D levels are low, supplementation may be warranted. Muscle relaxants may also help relieve symptoms.

9.1.4. Weight Loss

Decreased appetite or anorexia may result from use of bardoxolone methyl. Weight loss of approximately one kilogram per month may be observed, with patients of higher body-mass index at baseline losing more than those of normal or moderately-elevated body-mass index. Ongoing assessments to ensure that the patient is receiving adequate nutrition and consideration of other etiologies of weight loss may be warranted for patients receiving bardoxolone methyl.

9.1.5. Hypomagnesaemia

In instances where the patients experience hypomagnesaemia, defined as serum magnesium less than 1.3 mEq/L [0.65 mmol/L], consideration should be given to repletion of serum magnesium.

9.1.6. Nausea

Nausea may occur with higher doses of bardoxolone methyl. Nausea adverse events are typically mild and reversible within a few weeks after treatment initiation. If symptoms do not resolve, dose de-escalation, with consultation of the medical monitor, may be necessary.

9.1.7. Anemia

Anemia is a common occurrence in PAH patients. If a patient has serum levels of hemoglobin < 10.5 g/dL at Screening, the patient will be allowed to re-screen following anemia treatment. Re-screening can occur no sooner than 30 days following initiation of anemia treatment.

9.2. Description of Study Drug

Bardoxolone methyl (RTA 402) drug product information is shown in Table 7. Information about the placebo is shown in Table 8. Treatment kits containing bardoxolone methyl capsules, 2.5 mg, 5 mg, 10 mg, or 15 mg, or placebos to match these strengths are utilized in Part 1 of this study. Single or multiple 30 count or 90 count bottles of bardoxolone methyl capsules may be utilized in Part 2 of this study.

Table 7: Bardoxolone Methyl Drug Product Information

Description	Bardoxolone methyl capsules (2.5 mg, 5 mg, 10 mg, or 15 mg)
Ingredients	[redacted]
Route of Administration	[redacted]
Manufacturer	[redacted]

Table 8: Placebo Information

Description	Placebo to match bardoxolone methyl capsules (2.5 mg, 5 mg, 10 mg, or 15 mg)
Ingredients	[redacted]
Route of Administration	[redacted]
Manufacturer	[redacted]

9.3. Concomitant Medications

9.3.1. Excluded Medications

Patients taking these medications or treatments will be ineligible for enrollment or continuation in the study:

- Any other investigational drug or device studies;
- Intravenous (iv) or subcutaneous (sc) prostacyclin/prostacyclin analogue;
- Intravenous inotropes;
- Inhaled nitric oxide (excluding acute vasodilator testing during diagnostic cardiac catheterization).

9.3.2. Permitted Medications

Allowed concomitant medications include the following:

- Antibiotics;
- Daily multivitamins or recommended daily supplements;
- Other medications intended to manage concurrent diseases, as authorized by the treating physician;
- Medications intended to manage interstitial lung disease or sarcoidosis in patients enrolled in Cohort 4 (PH-ILD cohort), including but not limited to methotrexate, prednisone, nintedanib, or pirfenidone;
- Medications approved for treatment of WHO Group I PAH intended to manage pulmonary hypertension in WHO Group III and WHO Group V patients;
- Oral, implantable, or injectable contraceptives.

Patients taking medication chronically should be maintained on those same doses and dose schedules throughout the study period, as medically feasible.

The use of the following therapies, which may affect PH, are permitted during the study, provided the patients have been receiving a stable dosage for at least 30 days prior to Day 1. Unless medically indicated, the doses of these agents should remain unchanged during the study.

- Vasodilators (including calcium channel blockers);
- Digoxin;
- L-Arginine supplementation;
- Diuretics;
- Agents to treat anemia (including but not limited to supplemental iron, erythropoietin, or intravenous iron);
- If the patient receives intravenous iron therapy during Screening, the intravenous infusion must be performed at least 30 days prior to Day 1;

- Agents to treat neuropathic pain associated with peripheral neuropathy (such as pregabalin);
- Oxygen supplementation.

Corticosteroids are allowed if the patient has been receiving a stable dose of ≤ 20 mg/day of prednisone (or equivalent dose, if other corticosteroid) for at least 30 days prior to study Day 1. If receiving treatment for CTD with any other drugs, doses should remain stable for the duration of the study.

PAH-specific background therapy should be taken as clinically indicated and prescribed by the physician for the duration of the study.

Diuretics may be prescribed as clinically indicated throughout the study. Any changes to the doses of diuretics throughout the course of the study must be recorded in the eCRF.

Patients who fulfill the requirements, as defined above, should not be withdrawn from the study solely on this basis. Consultation with the medical monitor should occur prior to withdrawing a patient from the study.

9.4. Treatment Compliance

The Investigator or his/her designated and qualified representatives will only dispense study drug to patients enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol. A maximum of seven consecutive missed doses or no more than 14 missed days are permitted. Patients must be considered treatment compliant to be eligible for the extension period (Part 2).

9.5. Randomization

Patients will be assigned to cohort based on baseline 6MWD (i.e., ≤ 450 m versus > 450 m) for Cohorts 1 and 2, and based on PH classification for Cohorts 3 and 4. Cohort 3 includes two sub-cohorts (3a, 3b) and Cohort 4 includes 4 sub-cohorts (4a, 4b, 4c, 4d). Within each cohort (or sub-cohort), patients will be randomized to bardoxolone methyl or placebo for Part 1 of the study according to the treatment assignment regimen. Patients will be assigned to bardoxolone methyl in Part 2 according to the study design.

9.6. Blinding

In this double-blind study all patients, Investigators, site personnel, laboratories and central readers with direct involvement in the conduct of the study or their designees will be blinded to treatment assignments. Appropriate measures will be taken to ensure the blind is maintained for the patients and personnel mentioned previously to reduce potential bias. To maintain the blind, Investigators will distribute blinded study drug bottles to patients as directed by the IWRS system.

Treatment assignments will be managed by an IWRS system. The only people with direct access to treatment assignments will be those individuals who develop and maintain the randomization code, the individuals involved in the implementation and operation of the IWRS system, and the PSRC. Some Sponsor personnel will be unblinded to individual treatment assignments.

Upon starting Part 2 of the study (i.e., the extension phase) all patients will receive bardoxolone methyl.

9.6.1. Patient Unblinding

Although there is no known antidote to bardoxolone methyl, under rare circumstances unblinding may be considered medically necessary.

The investigator is encouraged to contact the medical monitor to discuss situations in which he or she believes that the blind should be broken, but the investigator has the right to break the blind (*e.g.*, in the event of a serious or life-threatening medical situation). If unblinding is required, the Investigator will utilize the IWRS to perform the unblinding. If a study drug assignment is unblinded, a description of the event that required unblinding must be documented by the Investigator in the patient's source documents.

Patients must discontinue taking study drug if their treatment assignment has been unblinded to the Investigator (or designee). Such patients must undergo the same early termination procedures as those patients who discontinue taking study drug for other reasons.

Patient treatment assignments must not be unblinded in the case of an AE or SAE, except as described above.

9.6.2. Unblinding for Regulatory Submission

In situations where regulation requires unblinding and reporting of a particular serious adverse event, the appropriate bodies (e.g., ethics committees, IRBs) must be provided with unblinded information according to the applicable regulatory requirement. This information must not be conveyed to Investigator, site personnel or patient; therefore, this type of unblinding does not necessitate that the patient discontinue taking study drug. In cases when unblinded information must be conveyed to local health authorities, personnel without direct involvement in the conduct of the study must be responsible for unblinding the patient's treatment using the IWRS and conveying the necessary information.

9.6.3. Protocol Safety Review Committee

A Protocol Safety Review Committee (PSRC) will assess the starting dose and each new dose level of bardoxolone methyl for safety and tolerability based on review of all available data for this study at the time of each review. PSRC reviews will occur after the Week 4 data are available for the first eight patients enrolled at each new dose level combined across Cohorts 1 and 2 (i.e., the 6MWD $\leq$ 450 m and 6MWD > 450 m cohorts). Upon completion of the dose ranging portion of the study, the PSRC will continue to meet at regular intervals (approximately quarterly) to monitor safety of all patients, including those enrolled in Cohorts 3 and 4.

The PSRC will include at a minimum a Sponsor representative, a cardiologist, and a statistician. Should issues arise requiring expertise not represented by the current members, the PSRC may appoint additional clinical specialists.

The PSRC will assess the following to escalate:

- Signs and symptoms of fluid overload, including adverse events (edema, dyspnea, etc.), weights, and BNP;
- All other collected safety laboratory test data and vital sign measurements;
- Pharmacodynamic markers of Nrf2 activation, including transaminase, GGT, and ferritin levels.

Doses or exposures associated with the defined dose levels in this protocol have been studied previously in healthy volunteers, oncology patients, patients with hepatic dysfunction, and patients with moderate CKD without untoward toxicity. Therefore, the PSRC will assess for general safety and specific signs and symptoms of fluid overload. The PSRC assessment will include a dose level recommendation based on clinical evaluation of the above specified assessments for subsequent cohorts to escalate to a higher dose, proceed to a lower dose, or maintain the current dose. The PSRC may also recommend stopping dosing for current cohorts.

9.7. Unscheduled Visits

Unscheduled visits are allowed for the following reasons:

- Assessment of weight gain as per Section 9.1.1;
- Management of an adverse event or serious adverse event;
- Performance of additional laboratory tests for clinically abnormal laboratory test values or to confirm a possible pregnancy;
- Dose de-escalation for patients enrolled in Cohorts 3 and 4;
- Dose escalation or dose de-escalation for patients enrolled in Cohorts 1 and 2 in Part 2 of the study;
- Any time the Investigator feels that it is clinically appropriate for patient safety.

Unscheduled visits may be performed as a home-health visit under the Investigator delegation and following prior sponsor approval.

9.8. Pregnancy

9.8.1. Women of Childbearing Potential

Women of childbearing potential (WOCBP) are those who are not surgically sterile (no history of bilateral tubal ligation, hysterectomy, or bilateral salpingo-oophorectomy) do not have fallopian inserts with confirmed blockage, have not had reproductive potential terminated by radiation, and are not postmenopausal for at least 1 year.

9.8.2. Methods of Birth Control

During screening, while taking study drug and until 30 days following administration of the final dose of study medication, WOCBP must practice one of the following methods of birth control:

- Use double barrier contraception method defined as male use of a condom and female use of a barrier method (e.g., contraceptive sponge, spermicidal jelly or cream, diaphragm [always use with spermicidal jelly/cream]);

- Use of hormonal contraceptives (oral, parenteral, vaginal, or transdermal) for at least 90 days prior to start of study drug administration;
- Use of an intrauterine device;
- Abstain from sexual intercourse completely. Complete abstinence from sexual intercourse is only acceptable if it is the preferred and usual lifestyle of the individual. Periodic abstinence is not permitted.

During screening, while taking study drug and until 30 days after the final dose of study medication is taken, males who have female partners of childbearing potential must practice one of the following methods of birth control:

- Have had a vasectomy (at least 6 months earlier);
- Use double barrier contraception method defined as male use of a condom and female use of a barrier method (e.g., contraceptive sponge, spermicidal jelly or cream, diaphragm [always use with spermicidal jelly/cream]);
- Partner use of an intrauterine device;
- Partner use of hormonal contraceptives (oral, parenteral, vaginal or transdermal) for at least 90 days prior to start of study drug administration;
- Abstain from sexual intercourse completely. Complete abstinence from sexual intercourse is only acceptable if it is the preferred and usual lifestyle of the individual. Periodic abstinence is not permitted.

9.8.3. Suspected Pregnancy

During the study, all WOCBP must be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., late or missed menstrual period). Male patients must be instructed to contact the Investigator if a sexual partner suspects she may be pregnant.

If a patient or Investigator suspects that the patient may be pregnant, the study drug must be withheld until the results of a serum pregnancy test are available. If pregnancy is confirmed with a serum pregnancy test result, the patient must permanently discontinue taking study drug. The Investigator must immediately report to the medical monitor a pregnancy associated with study drug exposure. The early discontinuation protocol-required procedures outlined for End-of-treatment and Follow-up visits must be performed on the patient.

Pregnancy is not considered an AE, however, the Investigator must follow a pregnant patient, or the pregnant female partner of a male patient (if consenting), and report follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants resulting from such pregnancies should be followed for a minimum of 8 weeks. Reata or designee may contact the Investigator to request additional information throughout the course of the pregnancy.

The following pregnancy outcomes must be considered SAEs and will require additional reporting in the eCRF and reported as a serious adverse event:

- Congenital anomaly/birth defect;

- Stillbirth;
- Spontaneous miscarriage.

9.9. Serious Toxicities

In the case of serious toxicities, the Investigator may choose to interrupt treatment with bardoxolone methyl. Dose reductions are permitted for patients enrolled in Cohorts 3 and 4, as well as patients enrolled in Part 2 of the study. Patients who resume therapy after an interruption will follow the originally planned study schedule. If the interruption of treatment with bardoxolone methyl exceeds 7 consecutive days or 14 total days, the patients should be discontinued from the study as outlined in Section 8.4.

9.10. Study Procedures

The following sections describe each assessment. The timing of these assessments is noted in Table 3 and Table 4 and Table 5 or Table 6. All Day 1 procedures, except AE assessments, should be completed prior to administration of first dose of study drug.

9.10.1. Informed Consent

Written informed consent (see Section 15.3) must be obtained from the patient before any study-related procedures are performed, and again if there is a change in the study procedures that would affect the patient's willingness to participate.

9.10.2. Inclusion/Exclusion

Inclusion and exclusion criteria should be reviewed at the times indicated in Table 3 or Table 4. Patients must meet all of the inclusion and none of the exclusion criteria for entry in the study. Investigators should contact the medical monitor with any questions regarding eligibility prior to randomizing the patient on Day 1.

9.10.3. Demographics and Baseline Disease Characteristics

Demographic data including sex, age, race, and ethnicity, will be collected at the times indicated in Table 3 or Table 4. Baseline disease characteristics will be collected at the time point indicated in Table 3 or Table 4.

9.10.4. Prior and Current Concomitant Medications

The name, dose, and frequency must be recorded for all medications that the patient is taking. All allowed and excluded medications should be recorded including all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Trade or generic drug names should be used where possible. Concomitant medications will be reviewed at the times indicated in Table 3 or Table 4 or Table 5 or Table 6 and all changes will be recorded.

9.10.5. Medical History

A complete medical history (e.g., per patient report) that includes all medical history within the past 5 years must be collected. Medical history will be recorded at the times indicated in Table 3 or Table 4.

9.10.6. Right Heart Catheterization

A right heart catheterization (RHC) completed prior to Day 1 is required. However, if a patient has not had a RHC completed prior to planned Day 1, it should be performed after the patient has signed Informed Consent and has passed the Screen A eligibility procedures.

In addition, data resulting from a RHC performed before Day 1 or during the course of the study as part of the patient's standard of care, should be collected on the patient's case report form. Other data resulting from procedures conducted as part of the standard of care for the patient that may contribute to the Sponsor's understanding of the safety or efficacy of the compound may also be requested.

9.10.7. Height

Height should be measured without footwear, head coverings or prosthetics at the time indicated in Table 3 or Table 4.

9.10.8. Weight and Body Mass Index (BMI)

Weight should be measured at the times indicated in Table 3 or Table 4 and Table 5 or Table 6. Body mass index (BMI) will be calculated in the eCRF each time the weight is recorded. The Sponsor will provide each patient with a scale to use at home to capture daily weights. Weights should be taken at the same time each day and recorded in a patient diary. During the first four weeks (Cohort 1 and 2) or first eight weeks (Cohort 3 and 4) of both Part 1 and Part 2, weights will be collected daily; weekly weights will be collected thereafter. Patients will be instructed to stop administering study drug and contact the Investigator if their daily weight increases as per the criteria outlined in Section 9.1.1. Patients will be provided instructions within the Informed Consent Form to help ensure consistent weight collection throughout the study.

9.10.9. Electrocardiograms (ECG)

A 12-lead ECG will be recorded after the patient has rested for at least 10 minutes in a supine position at the times indicated in Table 3 or Table 4 and Table 5 or Table 6. The heart rate from the ECG machine should not be used as part of the vital sign measurements.

9.10.10. Vital Sign Measurements

Vital sign measurements include the patient’s heart rate (beats/minute taken for at least 15 seconds), respiration rate, and oral or tympanic body temperature. Blood pressure should be taken after the patient has rested in a sitting position for at least 5 minutes. The same arm (usually the non-dominant arm) and the appropriate size cuff should be used for each measurement. Vital sign measurements should be taken at the times indicated Table 3 or Table 4 and Table 5 or Table 6. Resting oxygen saturation will be collected for patients enrolled in Cohort 3 and Cohort 4 (PH-ILD).

9.10.11. Ambulatory Blood Pressure Monitoring (ABPM)

ABPM will be performed on all Cohort 1 and Cohort 2 patients only in Part 1 of this study at the times indicated in Table 3. A Sponsor-provided device will be placed on the patient by site personnel with the appropriate training. Participants will wear the ABPM for a minimum of 24 hours. Patients should return to the clinic the next day to have the device removed; however, with prior sponsor approval, the monitor may be removed at least 24-hours after placement and returned to the Investigator. ABPM will not be collected in patients enrolled in Cohorts 3 and 4 (PH-ILD cohort).

9.10.12. Physical Examination

A comprehensive physical examination must be performed by a physician, physician assistant, or registered nurse practitioner at the time points indicated in Table 3 or Table 4 and Table 5 or Table 6 and as documented within the table footnotes. The examination must include the following organ or body system assessments: head, eyes, ears, nose, throat, musculoskeletal, cardiovascular, lymphatic, respiratory, abdomen, skin, extremities, and neurological. Assessments of any specific signs or symptoms reported by the patient must also be performed and documented along with any other findings of note. Findings at Screening must be characterized as either normal or abnormal, and if abnormal, a description of the abnormality must be provided. Following the examination at Screening, changes must be classified as new, worsened, or improved from the last time the body system was assessed. If possible, the same individual should perform each physical examination on a patient during the study.

9.10.13. Pregnancy Test

WOCBP (see Section 9.8) will complete a pregnancy test at the time points indicated in Table 3 or Table 4 and Table 5 or Table 6, or at any point in time if pregnancy is suspected. Negative test results are required on Day 1 before study drug administration. Any patient who becomes pregnant during the study must discontinue taking study drug immediately. See Section 9.8.3 for a description of procedures to be followed in case of pregnancy.

9.10.14. Study Drug Administration

Patients should self-administer the assigned number of capsules orally once a day in the morning at the time points indicated in Table 3 or Table 4 and Table 5 or Table 6. On days when PK samples are collected, patients should not self-administer study drug. Study staff will administer study drug at the clinic following collection of the first PK sample.

A vomited dose should not be replaced. Missed doses may be taken in the afternoon or evening of the same day. A double dose (e.g., missed dose from previous day and dose for current day) should not be taken.

For patients enrolled in Cohorts 3 and 4, as well as patients enrolled in Part 2 of the study, dose de-escalation may occur any time after a DLT occurs.

9.10.15. Study Drug Dispensation and Collection

Study drug will be dispensed to the patient and collected from the patient at the time points indicated in Table 3 or Table 4 and Table 5 or Table 6. For patients enrolled in Cohorts 3 and 4, dose escalation may occur at Week 4.

9.10.16. Telephone Contact

Patients will be contacted by telephone at the time points indicated in Table 3 or Table 4 and Table 5 or Table 6. Patients will be asked about their body weight and other signs of fluid retention. If fluid retention is suspected, the patient should be brought into the clinic and evaluated by the Investigator as soon as possible, as detailed in Section 9.1.1.

9.10.17. Adverse Event Collection

Patients should be observed for general appearance, presence of illness or injury, or signs indicative of a concurrent illness at the time points indicated in Table 3 or Table 4 and Table 5 or Table 6. Patients should be instructed to volunteer any information regarding AEs at any time during the study, or query the patients with an open question regarding any AEs they may be experiencing (e.g., "How have you been feeling since your last visit?"). Any findings are to be documented. They may also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (including prescription drugs, over-the-counter medications, vitamins, herbal products, and minerals). Responses must be documented in the source documents.

9.10.18. Clinical Chemistry

Samples will be collected for the following clinical chemistry analyses at the time points indicated in Table 3 or Table 4 and Table 5 or Table 6: ferritin, creatine kinase (CK), blood urea nitrogen (BUN), creatinine enzymatic, total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, sodium, potassium, calcium, phosphorus, uric acid, total protein, glucose, albumin, lactate dehydrogenase (LDH), magnesium, chloride, bicarbonate, gamma-glutamyl transpeptidase (GGT). An eGFR using the MDRD formula (eGFR = 175 x standardized serum creatinine $^{-1.154}$ x age $^{-0.203}$ x 1.212 [if black] x 0.742 [if female]) will be calculated at the Screen A visit only for eligibility purposes. Women of child-bearing potential will require a serum pregnancy test (hCG-Qual) at Screen A or at any point in time if a pregnancy is suspected.

9.10.19. N-Terminal Pro-Brain Natriuretic Peptide and Brain Natriuretic Peptide

Samples will be collected for NT-Pro BNP and BNP at the time points indicated in Table 3 or Table 4 and Table 5 or Table 6. As BNP and NT-Pro BNP may be affected by recent exercise, patients must be allowed to rest for a minimum period of one-hour following arrival at the clinic and prior to obtaining this blood sample. Similarly, this sample must be taken prior to the 6MWT. This sample should be taken with the patient in the same position at all appropriate visits, e.g., sitting or semi-recumbent.

After the Week 32 study visit, only NT-Pro BNP should be collected at study visits, as shown in Table 5 and Table 6.

Detailed instructions on collection, storage and shipment of the sample will be provided in the central laboratory manual provided to the Investigator.

9.10.20. Hematology

Samples will be collected for the following hematology assessments at the time points indicated in Table 3 or Table 4 and Table 5 or Table 6: hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, neutrophils, bands (if detected), lymphocytes, monocytes, basophils (if detected), eosinophils (if detected), absolute platelet count, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC).

9.10.21. Urinalysis and Microscopy

Samples will be collected for the following urinalysis and microscopy assessments at the time points indicated in Table 3 or Table 4 and Table 5 or Table 6: specific gravity, ketones, pH, protein, blood, glucose, clarity, color, leukocytes, nitrite, bilirubin, and a microscopic examination (if indicated based on laboratory results).

9.10.22. Virus Serology

Blood samples will be collected for testing for hepatitis B and hepatitis C at the time point indicated in Table 3 or Table 4.

9.10.23. 6-Minute Walk Test

A 6-minute walk test (6MWT) will be administered to patients at the time points indicated Table 3 or Table 4 and Table 5 or Table 6.

The 6MWT is a non-encouraged test that measures the distance walked over 6 minutes. The 6MWT must be performed consistently across all patients and sites. Therefore, each test must be performed in strict accordance with the instructions and script provided in Section 19 of Appendix 1, which are based on American Thoracic Society (ATS) guidelines [ATS Statement 2002]. The appropriate language version will be applied for patients with a non-English informed consent.

Patients who require supplemental oxygen with exercise may use their prescribed oxygen level during 6MWTs. The oxygen level administered during Screening should be used during all subsequent tests. Titration of supplemental oxygen levels used during the 6MWT should only occur during the Screening Visit 6MWT via the site's standard oxygen titration/administration processes. If a patient's health status deteriorates during study participation and it is determined by a physician that the patient requires additional supplemental oxygen, the patient may continue study participation. However, the original supplemental oxygen level used during the Screening Visit 6MWT should continue to be used during all subsequent 6MWTs. In the opinion of the investigator, if a patient's health status deteriorates to the point that the patient can no longer safely conduct subsequent 6MWTs using the original supplemental oxygen set at the Screening Visit, then 6MWT should not be conducted.

At the completion of every 6MWT, the Borg dyspnea index will be recorded as well as results of pulse oximetry. Patients should not carry the pulse oximeter during the 6MWT; instead, pulse oximetry is to be collected at the beginning and end of the 6MWT using a headband, ear or finger probe. For patients with scleroderma in Cohorts 3a and 4a, a finger probe pulse oximeter should not be used.

Investigators or appropriate 6MWT administrators should not walk with the patient during the test.

9.10.24. Echocardiography

A screening echocardiogram (ECHO) will be completed and read locally to determine eligibility. Day 1 and all subsequent ECHOs will be sent to a core lab for reading. Pulmonary vascular resistance (PVR) and other hemodynamic measures will be estimated using a Doppler echocardiogram (ECHO) following a standardized protocol-specific procedure described in a separate manual. ECHOs will be performed at the time points indicated in Table 3 or Table 4 and Table 5 or Table 6. Other than during screening, echocardiography assessments will not be collected in patients enrolled in Cohort 3 and Cohort 4.

[redacted]

9.10.26. Pulmonary Function Testing

Pulmonary Function Testing that includes forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), FEV1/FVC ratio (FEV1%), peak expiratory flow (PEF), tidal volume (TV), and total lung capacity (TLC) will be performed at the time points indicated in Table 3 or Table 4 and Table 5 or Table 6.

[redacted]

[redacted]

9.10.32. Clinical Worsening

The Investigator or authorized designee will evaluate clinical worsening at the time points indicated in Table 3 or Table 4 and Table 5 or Table 6. If clinical worsening is suspected, further clinic evaluations may be required to document the protocol-defined (listed below) clinical worsening event (CWE).

- Death, or onset of treatment-emergent AE with a fatal outcome occurring less than or equal to 14 days after study treatment discontinuation;
- Heart-lung or lung transplant, or hospitalization for lung transplant;
- Atrial septostomy, or hospitalization for atrial septostomy;
- The patient requires the addition of any of the following medications:
  - Prostacyclin/prostacyclin analogue (intravenous, subcutaneous, oral, or inhaled) except for acute vasodilator testing during cardiac catheterization
  - Intravenous inotropes for right ventricular failure with appropriate documentation
  - Phosphodiesterase type-5 inhibitors
  - Endothelin receptor antagonist

- Riociguat

- The combined occurrence of the events listed below. If a CWE is confirmed by these criteria, then an NT-pro BNP laboratory assessment is required on the day of the second 6MWT with the NT-Pro BNP sample obtained after 1 hour of rest:

  1. A decrease in 6MWT by at least 15% from Baseline, confirmed by two 6MWTs, on different days;

  AND

  2. Increase (worsening) ≥ 1 grade in WHO FC from Baseline;

  AND

  3. Appearance of or worsening of signs/symptoms of right heart failure that did not respond to optimized oral diuretic therapy.

In case of clinical deterioration the Investigator must assess carefully if the deterioration of the patient's condition (e.g., worsening functional class) is related to the underlying pulmonary hypertension or can be explained by an alternative cause (e.g., transient infection, musculoskeletal disease, surgical or medical intervention other than pulmonary hypertension-related, exacerbation of a concomitant lung disease, lacking compliance of medication intake). Only persistent clinical deteriorations caused by the underlying pulmonary arterial hypertension will be considered a clinical worsening event.

Time to clinical worsening will be evaluated as the number of days between randomization and the occurrence of a predefined clinical worsening event.

Transient deteriorations of clinical status requiring hospitalization, treatable by, for example, short-time application of intravenous diuretics, positive inotropic agents or non-invasive ventilation and allowing patients discharge within 48 hours, are not considered to meet the criteria for a CWE. Patients should be discontinued only if any of the above criteria exceed 48 hours.

9.10.33. WHO/NYHA Functional Class Assessment

WHO functional class assessment (Section 20, Appendix 2) will be made and documented at the time points indicated in Table 3 or Table 4 and Table 5 or Table 6 as well as at any time clinical worsening is suspected. WHO/NYHA FC will be assessed. To the extent feasible, the same evaluator should assess WHO/NYHA FC for a particular patient over the entire course of the study.

9.10.34. Pharmacokinetic (PK) Blood Samples

Blood samples for determination of plasma bardoxolone methyl and potential metabolite concentrations will be drawn at the time points indicated in Table 3 or Table 4 and Table 5 or Table 6. Patients will be asked by site personnel to provide the time of their last two study drug administrations prior to the blood samples being collected. This data will be based on patient recall and not collected in a patient diary. Blood sample collection instructions should be referenced in the laboratory manual.

The date and time of collection of all PK blood samples should be recorded; however, any deviations from the protocol-specified sampling times will not be considered protocol deviations. Sample time deviations will be summarized in the study report. Dates in the case report form should be recorded in an unambiguous format (e.g., DD MMM YYYY) and time should be recorded to the nearest minute (e.g., HH:MM using the 24-hour clock). Blood samples not drawn should be recorded as such.

[redacted]

9.10.38. High Resolution Computed Tomography (HRCT) Scan or Biopsy

A HRCT scan or biopsy to confirm presence of ILD must be completed prior to Day 1 is required for patients to enroll in Cohort 4. However, if a patient has not had a HRCT scan or biopsy completed prior to planned Day 1, it should be performed after the patient has signed Informed Consent and has passed the Screen A eligibility procedures.

[redacted]

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

Bardoxolone methyl capsules, 2.5 mg, 5 mg, 10 mg, and 15 mg, and placebos to match, will be used in this study.

10.2. Study Drug Packaging and Labeling

Kits will be dispensed during study Part 1 (Day 1 through Week 12 dispensing). Either bottles containing 30-count or 90-count of capsules or treatment kits will be dispensed during study Part 2. The extension period begins with the Week 16 dispensing. The blind will be maintained until the Week 20 dispensing.

During study Part 1, the study drug will be supplied in tamper-evident kits containing three 30-cc high-density polyethylene (HDPE) bottles and one 60-cc HDPE bottle. Each bottle will utilize foil induction-seal liners and a child-resistant closure. Each bottle of study drug will contain 30 count of 2.5 mg, 5 mg, or 15 mg strength bardoxolone methyl or corresponding placebo capsules. Each bottle will also contain a desiccant insert that must not be ingested. Labeling on each kit bottle will contain the following information:

- Medication ID number;
- Protocol 402-C-1302;
- Caution Statement: Limited to Investigational Use. Keep out of sight or reach of children;
- Store at 20° – 25°C (68° – 77°F), excursions allowed to 15° – 30°C (59° – 86°F);
- Reata Pharmaceuticals, Inc., Irving, TX.

During study Part 2, the study drug may also be supplied in 30-count or 90-count bottles with child-resistant closures. Additionally, labeling, in the relevant local languages for investigational medicinal product (IMP) for use and distribution in the EU shall adhere to current Eudralex, Volume 4 Annex 13 guidance and requirements.

10.3. Study Drug Storage

The stability of the drug product is being evaluated in ongoing studies.

Investigative sites must store the investigational product in a secure location with room temperature conditions of 20° - 25°C (68° - 77°F), excursions allowed to 15° – 30°C (59 –86°F).

10.4. Study Drug Administration

Please refer to Section 9.10.14 for details on study drug administration. Clear instructions will be provided to the patient regarding the number and type of capsules to be ingested at each study drug administration time point listed in Table 3 or Table 4 and Table 5 or Table 6. Patients must be instructed to continue taking study drug once daily up through their Week 16 visits unless otherwise instructed by the Investigator or been formally discontinued from the study. Patients entering the extension period will be instructed to continue taking bardoxolone methyl once daily

through the end of the study unless otherwise instructed by the Investigator or been formally discontinued from the study.

10.5. Study Drug Accountability

The Investigator, or designee, will maintain a record of all study drug received, dispensed, and returned to the Sponsor or its designee. No study drug shall be destroyed by the clinical site unless directed to do so by the Sponsor or its designee. Study drug bottles and any unused capsules should be returned to the study staff.

10.6. Study Drug Handling and Disposal

At the conclusion of the study, the Sponsor or its designee will direct the site regarding the final disposition of any remaining study drug.

11. SAFETY ASSESSMENTS

11.1. Safety Parameters

To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all safety assessments. Safety parameters include vital sign measurements, ECG results, 24-hour ambulatory blood pressure monitoring, physical examination results, adverse events, serious adverse events, weight and laboratory test results (clinical chemistry, hematology, urinalysis and microscopy).

11.2. Adverse and Serious Adverse Events

11.2.1. Definition of Adverse Events

11.2.1.1. Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient regardless of its causal relationship to study treatment. An AE can be any unfavorable and unintended sign (including any clinically significant abnormal laboratory test result), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study-drug related. Included in this definition are any newly-occurring events or previous condition that has increased in severity or frequency since the administration of study drug.

All AEs that are observed or reported by the patient during the study (from time of administration of the first dose at the Day 1 visit until the final visit indicated in Table 3 or Table 4 and Table 5 or Table 6, as appropriate) must be reported, regardless of their relationship to study drug or their clinical significance.

11.2.1.2. Serious Adverse Event

A serious adverse event (SAE) is any AE occurring at any dose and regardless of causality that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Is a congenital anomaly or birth defect in an offspring of a patient taking study drug;
- Is an important medical event.

The term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Important medical events are those that may not meet any of the criteria defined above, however, they may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the SAE definition.

Pregnancy is not considered an AE; however, information will be collected for any pregnancies which occur during the study (from the time of the first dose of study drug until the final visit indicated in Table 3 or Table 4 and Table 5 or Table 6, as appropriate). Certain pregnancy outcomes will require submission as an SAE (See Section 9.8).

The Investigator is responsible for reporting to Reata or designee all AEs and SAEs that are observed or reported by the patient during the study (from the time of administration of the first dose of study drug until the final visit indicated in Table 3 or Table 4 and Table 5 or Table 6, as appropriate), regardless of their relationship to study drug or their clinical significance. All SAEs reported or observed during the study must be followed to resolution or until the Investigator deems the event to be chronic or the patient to be stable. Reata or designee may contact the Investigator to obtain additional information on any SAE which has not resolved at the time the patient completes the study.

11.3. Eliciting Adverse Event Information

At every study visit, patients must be asked a standard, non-directed question, such as, "How have you been feeling since your last visit?" to elicit any medically related changes in their well-being. They may also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (including prescription drugs, over-the-counter medications, vitamins, herbal products, and minerals). Responses must be documented in the source documents.

In addition to patient observations, AEs must be documented for any clinically significant diagnosis resulting from abnormal laboratory test values, physical examination findings, or ECG abnormalities, or from other documents that are relevant to patient safety.

11.4. Assessment of Causality

The Investigator must use the following classifications and criteria to characterize the relationship or association of the study drug in causing or contributing to the AE:

Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

Unlikely: This relationship suggests that the temporal sequence of the event with study drug administration makes a causal relationship improbable and/or other factors also provide plausible explanations.

Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE. That is, the event follows a reasonable temporal sequence from the time of study drug administration, and/or, follows a known response pattern to the study drug, but could have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with study drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the Investigator's clinical experience, the association of the event with study drug administration seems likely.

11.5. Assessment of Severity

The Investigator will grade the severity of the AEs as mild, moderate, or severe using the following definitions:

Mild: Symptoms causing no or minimal interference with usual social and functional activities

Moderate: Symptoms causing greater than minimal interference with usual social and functional activities

Severe: Symptoms causing inability to perform usual social and functional activities.

11.6. Recording Adverse Events

All conditions present prior to the administration of the first dose of study drug (Day 1) should be documented as medical history. After the first dose, documentation of adverse events (AEs) shall continue until 30 days following administration of the final dose of study medication, regardless of the relationship of the AE to study drug. Information to be collected includes type of event, date of onset, date of resolution, Investigator-specified assessment of severity and relationship to study drug, seriousness, as well as any action taken.

While an AE is ongoing, changes in the severity (e.g., worsening and improving) should be noted in the source documents, but when documenting the AE, only the total duration and greatest severity should be recorded in the eCRF. AEs characterized as intermittent require documentation of onset and duration.

All drug-related (Possible or Probable, see Section 11.4) AEs and abnormal laboratory test results reported or observed during the study must be followed to resolution (either return to baseline or within normal limits). All other AEs will be followed through the final visit indicated in Table 3 or Table 4 and Table 5 or Table 6, as appropriate.

AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. Preexisting conditions (present before the start of the AE collection period) are considered concurrent medical conditions and should NOT be recorded as AEs. However, if the patient experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…"). Any improvement in condition should be documented as per Section 9.10.12.

Each AE should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory test values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded as an AE(s). Changes in laboratory test values or ECG parameters are only considered to be AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiological fluctuation). If abnormal laboratory test values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine levels in renal failure), only the diagnosis should be reported as an AE.

Elective procedures (surgeries or therapies) that were scheduled prior to the start of AE collection are not considered AEs. These elective procedures should not be recorded as AEs, but should be documented in the patient's source documents as elective (e.g., elective periodontal surgery). However, if a pre-planned procedure is performed early (e.g., as an emergency) because of a worsening of the preexisting condition, the worsening of the condition should be captured as an AE.

11.7. Reporting Serious Adverse Events

Any AE the Investigator considers serious according to the previously described criteria must be reported within 24 hours from the time the site personnel first learn about the event.

To report the SAE, fax the completed SAE form to Medpace (fax number listed below) within 24 hours of awareness.

Table 9: SAE Reporting Contact Information

Medpace SAE hotline North America and Australia Telephone: [redacted] Facsimile: [redacted] E-mail: [redacted] Medpace SAE hotline Europe Telephone: [redacted] Facsimile: [redacted]

For questions regarding SAE reporting, contact your study manager, monitor, or Medpace Clinical Safety.

Follow-Up Reports

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment) or the subject dies.

Within 24 hours of receipt of new information, the updated follow-up SAE form, along with any supporting documentation (e.g., subject discharge summary or autopsy reports), should be faxed to Medpace Clinical Safety.

The Sponsor or designee will notify regulatory agencies of any fatal or life-threatening unexpected events associated with the use of the study drug as soon as possible but no later than 7 calendar days after the initial receipt of the information. Initial notification will be followed by a written report within the timeframe established by the appropriate regulatory agency. For other SAEs that do not meet the fatal or life-threatening unexpected criteria, but are reported to be associated with the use of the study drug, Reata or designee will notify the appropriate regulatory agencies in writing within the timeframe established by those regulatory agencies. Reata or designee will provide copies of any reports to regulatory agencies regarding serious and

unexpected SAEs to the Investigators for review and submission to their institutional review board (IRB) or Ethics Committee (EC), as appropriate.

Principal Investigators are responsible for informing their IRB/EC of any SAEs at their site. SAE correspondence with regulatory authorities or IRBs/ECs must be submitted to the Sponsor or designee for recording in the study file.

Note that the following adverse events which are commonly observed in this patient population will not be reported to regulatory authorities as individual expedited reports, except in unusual circumstances.

- Shortness of breath
- Lightheaded/dizzy
- Syncope
- Chest pain
- Palpitations
- Fatigue
- Edema/fluid retention
- Exertional dyspnea
- Hypoxemia

These events will be reviewed on a regular basis in aggregate and will be reported in an expedited manner if a safety signal is detected. Regular safety study updates will be reported to regulatory authorities according to local guidelines.

12. STATISTICS

12.1. Sample Size

A sample size of 8 patients randomized at a 3:1 (bardoxolone methyl:placebo) assignment ratio in each dose level (Cohorts 1 and 2) includes 6 patients treated with bardoxolone methyl for identification of gross safety signals. A small number of patients at each dose is not expected to fully characterize safety, therefore issues of concern identified in only 1 of 6 patients (16%) treated with bardoxolone methyl may suggest the need to collect additional information before escalating the dose, by either adding another cohort at the current dose level or a lower dose as determined by the PSRC. Enrollment of patients at each additional dose level adds 6 more patients treated with bardoxolone methyl to further characterize safety, tolerability, and efficacy.

[redacted]

12.2. Study Variables

12.2.1. Pharmacokinetic Variables

The pharmacokinetic variables include bardoxolone methyl plasma concentration-time data, metabolite concentration-time data (if available), and estimated pharmacokinetic parameters for each analyte.

12.2.2. Efficacy Variables

The primary efficacy variable is the change from baseline in 6MWD. [redacted]

12.2.3. Safety Variables

The safety variables include ECGs, vital sign measurements, ABPM, results of physical examinations, laboratory test results (clinical chemistry, hematology, urinalysis and microscopy), concomitant medications, adverse events, and serious adverse events.

12.3. Statistical Analyses

A statistical analysis plan (SAP) detailing the analyses will be developed prior to the database lock. All statistical analyses and data summaries will be performed using SAS® (Version 9.1 or higher) or other similar software. The SAP will serve as the final arbiter of all statistical analyses. Data will be summarized overall using descriptive statistics. Continuous data will be summarized with number of patients (n), mean, median, minimum, maximum, standard deviation, coefficient of variation, and geometric mean (where applicable). Categorical data will be summarized using frequency counts and percentages.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

The study monitor, as a representative of the Sponsor, has the obligation to follow the study conduct closely. In doing so, the monitor will visit the principal Investigator and study facilities periodically, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current knowledge of the study activity of the Investigator and his/her staff through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigators and staff.

The Sponsor or designee will monitor all aspects of the study for compliance with applicable government regulation with respect to the International Conference on Harmonisation (ICH) guideline E6(R1): Good Clinical Practice: Consolidated Guideline and current standard operating procedures.

Each Investigator is expected to make a reasonable effort to accommodate the monitor when monitoring visits are necessary and to be available during the site visit. Furthermore, the monitor should be provided direct access to source data and documents for trial-related monitoring and internet during the visit.

13.2. Audits and Inspections

Principal Investigators and institutions involved in the study will permit study-related monitoring, audits, and IRB/EC review, and regulatory inspection(s), by providing direct access to all study records. In the event of an audit, the principal Investigator agrees to allow the Sponsor, representatives of the Sponsor, the US Food and Drug Administration (FDA), or other relevant regulatory authorities access to all study records.

The principal Investigator should promptly notify the Sponsor or designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor or designee.

14. QUALITY CONTROL AND QUALITY ASSURANCE

14.1. Quality Assurance

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Reata may conduct a quality assurance audit.

14.2. Financial Disclosure

Principal Investigators and sub-Investigators are required to provide financial disclosure information prior to starting the study. In addition, the principal Investigator and sub-Investigators must provide the Sponsor or designee with updated information, if any relevant changes occur during the course of the investigation and for one year following the completion of the study.

Any potential Investigator who has a vested financial interest in the success of this study may not participate in this study.

14.3. Sponsor Obligations

The Sponsor or designee is not financially responsible for further testing/treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, the Sponsor or designee is not financially responsible for treatment of the patient's underlying disease.

14.4. Investigator Documentation

Before beginning the study, the principal Investigator will be asked to comply with ICH E6(R1) 8.2 and Title 21 of the Code of Federal Regulations (CFR) by providing the essential documents to the Sponsor or designee, which include but are not limited to the following:

- An original Investigator-signed Investigator agreement page of the protocol;
- The IRB/EC approval of the protocol;
- The IRB- or EC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardians;
- A Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572;
- Curricula vitae for the principal Investigator and each sub-Investigator listed on Form FDA 1572. A curricula vitae and current licensure, as applicable, must be provided. The curricula vitae must have been signed and dated by the principal Investigators and sub-Investigators within 2 years before study start-up to indicate the documents are accurate and current;
- Completed financial disclosure forms (Section 14.2) to allow the Sponsor or designee to submit complete and accurate certification or disclosure statements required under US Title 21 CFR 54. In addition, the Investigators must provide to the Sponsor or designee a commitment to update this information promptly if any relevant changes

occur during the course of the investigation and for 1 year following the completion of the study;

- Laboratory certifications and normal ranges for any laboratories used by the site for the conduct of this study.

14.5. Clinical Study Insurance

In accordance with the respective national drug laws, the Sponsor has taken out patient liability insurance for all patients who give their consent and enroll in this study. This insurance covers potential fatalities, physical injuries, or damage to health that may occur during the clinical study.

14.6. Use of Information

All information regarding bardoxolone methyl supplied by Sponsor to the Investigator is privileged and confidential. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. Furthermore, the Investigator is obligated to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of bardoxolone methyl and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

15. ETHICS

15.1. Institutional Review Board (IRB) or Ethics Committee Review

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/EC before study start. Each Investigator must provide the Sponsor or its designee a signed and dated statement that the protocol and informed consent have been approved by the IRB/EC for that site before consenting patients. Prior to study initiation, the Investigator is required to sign a protocol signature page confirming agreement to conduct the study in accordance with this protocol and to give access to all relevant data and records to the Sponsor, its designee, and regulatory authorities as required.

The IRB/EC chairperson or designee must sign all IRB/EC approvals and must identify the IRB/EC by name and address, the clinical protocol, and the date approval and/or favorable opinion was granted.

The principal Investigator is responsible for obtaining reviews of the clinical research at intervals specified by the IRB/EC, but not exceeding 1 year. The principal Investigator must supply the Sponsor or designee with written documentation of reviews of the clinical research.

15.2. Ethical Conduct of the Study

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (e.g., US Code of Federal Regulations Title 21, European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

The principal Investigator agrees to conduct the study in accordance with the International Conference on Harmonization (ICH) for Guidance for Industry on Good Clinical Practice (GCP) ICH E6(R1) [http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf] and the principles of the Declaration of Helsinki [http://www.wma.net/en/30publications/10policies/b3/]. The principal Investigator must conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

15.3. Written Informed Consent

Because the study will be conducted under a United States Investigational New Drug Application, a signed informed consent form, in compliance with Title 21 of the United States Code of Federal Regulations (CFR) Part 50, will be obtained from each patient before the patient enters the study. For sites outside of the United States, the signed consent will be obtained in accord with local regulations, ICH E6 (R1), and principles of the Declaration of Helsinki. An informed consent template may be provided by the Sponsor or designee to the Investigators. The consent must be reviewed by the Sponsor or designee before IRB/EC submission. Once reviewed, the consent will be submitted by the principal Investigator to his or her IRB/EC for review and approval before the start of the study. If the informed consent form is revised during the course of the study, all participants affected by the revision must sign the revised IRB/EC-approved consent form.

Before enrollment, each prospective patient will be given a full explanation of the study and be allowed to read the approved informed consent form. Once the principal Investigator or designee is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing the informed consent form.

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/EC-approved informed consent. Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Any changes to the proposed consent form suggested by the Investigator must be agreed to by the Sponsor before submission to the IRB/EC, and a copy of the approved version and the notice of approval must be provided to the Sponsor's designated monitor after IRB/EC approval.

The principal Investigator or designee will provide a copy of the informed consent form (signed copy to be provided per applicable law) to the patient and/or legal guardian. The original form will be maintained in the patient's medical records at the site.

15.4. Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, the FDA or applicable regulatory authorities, or the IRB/EC.

The principal Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished confidential information disclosed to them for the purpose of the study. Prior written agreement from the Sponsor or designee must be obtained for the disclosure of any said confidential information to other parties.

15.5. Modification of the Protocol

Any changes, which arise after the approval of the protocol, must be documented as protocol amendments. FDA or other applicable regulatory agencies must be notified of protocol amendments. The changes will become effective only after approval of the Sponsor, the Investigator, the IRB/EC, and where necessary, the applicable regulatory agency. In cases when the protocol is modified to enhance patient safety, changes may be implemented and the amendment must be immediately submitted to the IRB/EC.

The Investigator is responsible for informing the IRB/EC of all problems involving risks to patients according to national legislation. In case of urgent safety measures, the Sponsor will immediately notify the Investigators and relevant regulatory agencies, including FDA in accord with 21 CFR 312.32.

15.6. Protocol Deviations

The principal Investigator or designee must document any protocol deviation. The IRB/EC must be notified of all protocol deviations in a timely manner by the principal Investigator or designee as appropriate. Protocol deviations will be documented by the responsible monitor during monitoring visits, and those observations will be communicated to the Investigator.

If there is an immediate hazard to a patient the principal Investigator may deviate from the protocol without prior Sponsor and IRB/EC approval. The Sponsor and IRB/EC must be notified of the deviation.

16. DATA HANDLING AND RECORDKEEPING

16.1. Retention of Records

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application submission or 2 years after formal discontinuation of the clinical development of the investigational product. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

16.2. Case Report Forms

All case report form data will be entered in paper or electronic forms at the investigational site. If an Electronic Data Capture system (EDC) is used to capture data electronically for all randomized patients, it will be 21 CFR Part 11 compliant.

17. PUBLICATION POLICY

The Sponsor reserves the right to review all planned communications and manuscripts based on the results of this study. This reservation of the right is not intended to restrict or hinder publication or any other dissemination of study results, but to allow the Sponsor to confirm the accuracy of the data, to protect proprietary information, and to provide comments based on information that may not yet be available to the study Investigators. The Sponsor supports communication and publication of study results whatever the findings of the study. The Sponsor also encourages disclosure of any conflict of interest from all authors or Investigators when manuscripts are submitted for publication. Those individuals, who have contributed greatly to this study, including lead external advisors and select principal Investigators, may serve on the publications committee for the study.

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19. APPENDIX 1: 6-MINUTE WALK TEST INSTRUCTIONS

(Modified from American Thoracic Society (ATS) Statement: Guidelines for the Six-Minute Walk Test. [ATS Statement 2002])

PURPOSE AND SCOPE

This statement provides practical guidelines for the 6-minute walk test (6MWT). Specifically, it reviews indications, details factors that influence results, presents a brief step-by-step protocol, outlines safety measures, describes proper patient preparation and procedures, and offers guidelines for clinical interpretation of results.

STUDY SPECIFIC REQUIREMENTS

The assessor of the 6MWT must not provide the patient with the results of the assessment once complete.

BACKGROUND

The 6MWT is a practical simple test that requires a 98-ft (30 meter) hallway but no exercise equipment or advanced training for technicians. Walking is an activity performed daily by all but the most severely impaired patients. This test measures the distance that a patient can walk on a flat, hard surface in a period of 6-minutes (the 6MWT). It evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism. It does not provide specific information on the function of each of the different organs and systems involved in exercise or the mechanism of exercise limitation, as is possible with maximal cardiopulmonary exercise testing. The self-paced 6MWT assesses the submaximal level of functional capacity. Most patients do not achieve maximal exercise capacity during the 6MWT; instead, they choose their own intensity of exercise and are allowed to stop and rest during the test. However, because most activities of daily living are performed at submaximal levels of exertion, the 6MWT may better reflect the functional exercise level for daily physical activities.

CONTRAINDICATIONS

Absolute contraindications for the 6MWT include the following: unstable angina during the previous month and myocardial infarction during the previous month. Relative contraindications include a resting HR of more than 120, a sBP of more than 180 mmHg, and a dBP of more than 100 mmHg.

Patients with any of these findings should be referred to the physician ordering or supervising the test for individual clinical assessment and a decision about the conduct of the test. The results from a resting electrocardiogram done during the previous 6 months should also be reviewed before testing. Stable exertional angina is not an absolute contraindication for a 6MWT, but patients with these symptoms should perform the test after using their antiangina medication, and rescue nitrate medication should be readily available.

Rationale
Patients with the previously mentioned risk factors may be at increased risk for arrhythmias or cardiovascular collapse during testing. However, each patient determines the intensity of their exercise, and the test (without electrocardiogram monitoring) has been performed in thousands of older persons and thousands of patients with heart failure or cardiomyopathy without serious adverse events. The contraindications listed previously here were used by study Investigators based on their impressions of the general safety of the 6MWT and their desire to be prudent, but it is unknown whether adverse events would occur if such patients performed a 6MWT; they are, therefore, listed as relative contraindications.

SAFETY ISSUES

1. Testing should be performed in a location where a rapid, appropriate response to an emergency is possible. The appropriate location of a crash cart should be determined by the physician supervising the facility.
2. Supplies that must be available include oxygen, sublingual nitroglycerine, aspirin, and albuterol (metered dose inhaler or nebulizer).
3. A telephone or other means should be in place to enable a call for help.
4. The technician should be certified in cardiopulmonary resuscitation with a minimum of Basic Life Support by an American Health Association–approved cardiopulmonary resuscitation course. Advanced cardiac life support certification is desirable. Training, experience, and certification in related health care fields (registered nurse, registered respiratory therapist, certified pulmonary function technician, etc.) are also desirable. A certified individual should be readily available to respond if needed.
5. Physicians are not required to be present during all tests. The physician ordering the test or a supervising laboratory physician may decide whether physician attendance at a specific test is required.
6. If a patient is on chronic oxygen therapy, oxygen should be given at their standard rate or as directed by a physician or a protocol.

Reasons for immediately stopping a 6MWT include the following: (*1*) chest pain, (*2*) intolerable dyspnea, (*3*) leg cramps, (*4*) staggering, (*5*) diaphoresis, and (*6*) pale or ashen appearance.

Technicians must be trained to recognize these problems and the appropriate responses. If a test is stopped for any of these reasons, the patient should sit or lie supine as appropriate depending on the severity or the event and the technician's assessment of the severity of the event and the risk of syncope. The following should be obtained based on the judgment of the technician: BP, pulse rate, oxygen saturation, and a physician evaluation. Oxygen should be administered as appropriate.

TECHNICAL ASPECTS OF THE 6MWT

Location
The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The walking course must be 15-30m in length. An approximate 49 to 98-ft hallway is, therefore, required. The length of the corridor should be marked every 3 meters. The turnaround points should be marked with a cone (such as an orange

traffic cone). A starting line, which marks the beginning and end of each lap, should be marked on the floor using brightly colored tape.

Rationale
A shorter corridor requires patients to take more time to reverse directions more often, reducing the 6MWT.

REQUIRED EQUIPMENT

1. Countdown timer (or stopwatch)
2. Mechanical lap counter
3. Two small cones to mark the turnaround points
4. A chair that can be easily moved along the walking course
5. Worksheets on a clipboard
6. A source of oxygen
7. Sphygmomanometer
8. Telephone
9. Automated electronic defibrillator

PATIENT PREPARATION

1. Comfortable clothing should be worn.
2. Appropriate shoes for walking should be worn. A notation should be made in the patient's source documentation of which shoes the patient wore for the first test. Prior to each clinic visit the patient should be called/reminded to ensure they wear this same pair of shoes.
3. Patients should use their usual walking aids during the test (cane, walker, etc.). NOTE – if a patient uses a walking aid for the first test this same aide should be used during all subsequent test whether needed or not.
4. The patient's usual medical regimen should be continued. The patient should continue to take doses of study drug prior to the test.
5. A light meal is acceptable before early morning or early afternoon tests.
6. Patients should not have exercised vigorously within 2-hours of beginning the test.

MEASUREMENTS

1. Repeat testing should be performed about the same time of day to minimize intraday variability.
2. A "warm-up" period before the test should not be performed.
3. The patient should sit at rest in a chair, <u>located at the starting position</u>, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and BP, and make sure that clothing and shoes are appropriate. Also, note the patient's general conditions and ailments (i.e. physical or mental) on this day that may potentially influence the results of the test. Complete the first portion of the course document worksheet.
4. Pulse oximetry is optional. If it is performed, measure and record baseline HR and pulse oximetry oxygen saturation (SpO_2) and follow manufacturer's instructions to maximize the

signal and to minimize motion artifact. Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable.

The rationale for measuring oxygen saturation is that although the distance is the primary outcome measure, improvement during serial evaluations may be manifest either by an increased distance or by reduced symptoms with the same distance walked. The SpO_2 should not be used for constant monitoring during the exercise. The technician must not walk with the patient to observe the SpO_2. If worn during the walk, the pulse oximeter must be lightweight (less than 2 pounds), battery powered, and held in place (perhaps by a "fanny pack") so that the patient does not have to hold or stabilize it and so that stride is not affected. Many pulse oximeters have considerable motion artifact that prevents accurate readings during the walk.

1. Set the lap counter to zero and the timer to 6-minutes. Assemble all necessary equipment (lap counter, timer, clipboard, Borg Scale, worksheet) and move to the starting point.
2. Instruct the patient as follows:

"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

Demonstrate by walking one lap yourself. Walk and pivot **around** a cone briskly.

"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6-minutes, but don't run or jog. Start now, or whenever you are ready."

1. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.
2. **Do not talk to anyone during the walk.** Use an **even tone of voice** when using the standard phrases of encouragement. Watch the patient. **Do not get distracted and lose count of the laps.** Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.
3. Investigators or appropriate 6MWT administrators should not walk with the patient during the test.

After the first minute, tell the patient the following (in even tones): *"You are doing well. You have 5-minutes to go."*

When the timer shows 4-minutes remaining, tell the patient the following: *"Keep up the good work. You have 4-minutes to go."*

When the timer shows 3-minutes remaining, tell the patient the following: *"You are doing well. You are halfway done."*

When the timer shows 2-minutes remaining, tell the patient the following: *"Keep up the good work. You have only 2-minutes left."*

When the timer shows only 1-minute remaining, tell the patient the following: *"You are doing well. You have only 1-minute to go."*

Do not use other words of encouragement (or body language to speed up).

If the patient stops walking during the test and needs a rest, say this: *"You can lean against the wall if you would like; then continue walking whenever you feel able."* **Do not stop the timer**. If the patient stops before the 6-minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

When the timer is 15 seconds from completion, say this: *"In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."*

When the timer rings (or buzzes), say this: *"Stop!"* Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

1. Post-test: Record the post-walk Borg dyspnea and fatigue levels and ask this: "What, if anything, kept you from walking farther?"
2. If using a pulse oximeter, measure SpO_2 and pulse rate from the oximeter and then remove the sensor.
3. Record the number of laps from the counter (or tick marks on the worksheet).
4. Record the additional distance covered (the number of meters in the final, partial lap) using the markers on the wall as distance guides.
5. Calculate the total distance walked, rounding to the nearest meter (i.e. 251.3 meters is 251 meters or 251.5 meters is 252 meters), and record it on the worksheet.
6. Congratulate the patient on good effort and offer a drink of water.

QUALITY ASSURANCE

Sources of Variability

There are many sources of 6MWT variability. The sources of variability caused by the test procedure itself should be controlled as much as possible. This is done by following the standards found in this document and by using a quality-assurance program.

Technician Training and Experience

Technicians who perform 6MWT should be trained using the standard protocol and then

supervised for several tests before performing them alone. They should also have completed cardiopulmonary resuscitation training.

Encouragement
Only standardized phrases for encouragement (as outlined above) must be used during the test.

Rationale
Encouragement significantly increases the distance walked. Reproducibility for tests with and without encouragement is similar. We have chosen every minute and standard phrases.

Supplemental Oxygen
Patients who require supplemental oxygen with exercise may use their prescribed oxygen level during 6MWTs. The oxygen level administered during Screening should be used during all subsequent tests. Titration of supplemental oxygen levels used during the 6MWT should only occur during the Screening Visit 6MWT via the site's standard oxygen titration/administration processes. Measurements of pulse and SpO_2 should be made after waiting at least 10-minutes after any change in oxygen delivery. If a patient's health status deteriorates during study participation and it is determined by a physician that the patient requires additional supplemental oxygen, the patient may continue study participation. However, the original supplemental oxygen level used during the Screening Visit 6MWT should continue to be used during all subsequent 6MWTs. In the opinion of the investigator, if a patient's health status deteriorates to the point that the patient can no longer safely conduct subsequent 6MWTs using the original supplemental oxygen set at the Screening Visit, then 6MWT should not be conducted.

The type of oxygen delivery device should also be noted on the report: for instance, the patient carried liquid oxygen or pushed or pulled an oxygen tank, the delivery was pulsed or continuous, or a technician walked behind the patient with the oxygen source (not recommended).

Pulse Oximetry
Patients should not carry the pulse oximeter during the 6MWT; instead, pulse oximetry is to be collected at the beginning and end of the 6MWT using a headband, ear or finger probe. For patients with scleroderma in cohorts 3a and 4a, a finger probe pulse oximeter should not be used.

20. APPENDIX 2: FUNCTIONAL CLASSIFICATION OF PULMONARY HYPERTENSION MODIFIED AFTER THE NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION ACCORDING TO THE WHO 1998 (GALIE 2009)

World Health Organization functional assessment classification	
Class I:	Patients with pulmonary hypertension (PH) 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 PH 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 PH 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 PH 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 physical activity.