RTA 402

402-C-1504

[redacted]

A STUDY OF THE EFFICACY AND SAFETY OF BARDOXOLONE METHYL IN PATIENTS WITH CONNECTIVE TISSUE DISEASE-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION

VERSION 2.0 – 18 OCT 2016

SPONSOR APPROVAL AND SIGNATURE PAGE

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for bardoxolone methyl. I have read the 402-C-1504 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 Study of the Efficacy and Safety of Bardoxolone Methyl in Patients with Connective Tissue Disease-Associated Pulmonary Arterial Hypertension

Study center(s): Approximately 100 study centers

Studied period: 24 months Estimated date first patient enrolled: October 2016 Estimated date last patient completed: October 2018	**Phase of development:** 3

Objectives:
For patients with connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) enrolled in this study, the objectives are as follows:

Primary:

- To assess the efficacy of bardoxolone methyl relative to placebo.

Secondary:

- To assess the safety of bardoxolone methyl relative to placebo.

Endpoints:

Primary Efficacy Endpoint:
Change from baseline in six-minute-walk distance (6MWD) relative to placebo at Week 24

Secondary Efficacy Endpoint:
Time-to-first clinical improvement event consisting of a persistent change for any of the following:

- Improvement by at least one WHO functional class
- Increase from baseline in 6MWD by at least 10%
- Decrease from baseline in creatine kinase (as a surrogate biomarker for muscle injury and inflammation) by at least 10%

Exploratory Efficacy Endpoint:

[redacted]

Safety:

Frequency, intensity, and relationship to study drug of adverse events and serious adverse events, and change from baseline in the following assessments: physical examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), clinical laboratory measurements, and weight.

Additional Exploratory Endpoints:

[redacted]

Methodology:

This double-blind, randomized, placebo-controlled trial will study the safety, tolerability, and efficacy of bardoxolone methyl in qualified patients with WHO Group I CTD-PAH.

Qualified patients will be randomized 1:1 to either bardoxolone methyl or placebo to be administered once daily for 24 weeks. Patients randomized to placebo will remain on placebo throughout the study. Patients randomized to bardoxolone methyl will start at 5 mg and will dose-escalate to 10 mg at Week 4 unless contraindicated clinically. Dose de-escalation is permitted during the study if indicated clinically. Please refer to Section 7.3.1 for additional details on dose escalation and dose de-escalation.

All patients in the study will follow the same visit and assessment schedule. Following randomization, patients will be scheduled to be assessed in person during treatment at Weeks 1, 2, 4, 6, 8, 16, and 24 and by telephone contact on Days 3, 10, 21, 31, 38, 84, and 140. Patients will also be scheduled to be assessed at an in person follow up visit at Week 28, four weeks after the end of treatment.

Patients who complete the study and are treatment-compliant to their assigned dose will be eligible for a separate open-label extension study.

Number of patients (planned):

Approximately 130 patients will be enrolled; this number may be increased up to approximately 200 patients based upon a blinded sample size re-calculation.

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/NYHA FC class II and III;
4. WHO Group I PAH associated with connective tissue disease;
5. Had a diagnostic right heart catheterization performed and documented within 36 months prior to Day 1 that confirmed a diagnosis of PAH according to all the following criteria:
    a. Mean pulmonary artery pressure ≥ 25 mm Hg (at rest);
    b. Pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg;
    c. Pulmonary vascular resistance > 240 dyn•sec/cm^5 or > 3 mm Hg/liter (L)/minute;
6. Has BNP level ≤ 400 pg/mL;
7. Had an average 6MWD ≥ 150 meters on two consecutive tests performed on different days prior to randomization, with a percent difference ≤ 15% between tests;
8. Has been receiving no more than two (2) approved disease-specific PAH therapies. PAH

therapy must have been at a stable dose for at least 90 days prior to Day 1. No additions or changes should be made to PAH therapies and doses should remain stable for the duration of the study;

9. Has maintained a stable dose for 30 days prior to Day 1 if receiving therapies that may affect walking distance, including but not limited to: vasodilators (including calcium channel blockers), digoxin, L-arginine supplementation, oxygen supplementation, diuretics, agents to treat neuropathic pain associated with peripheral neuropathy (such as pregabalin), and/or agents to treat anemia (such as 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;
10. If receiving treatment for CTD with prednisone or any other drugs, the medications must remain the same for at least 90 days prior to Day 1. Doses for medications prescribed for the treatment of CTD must remain stable for at least 30 days prior to Day 1 and for the duration of the study;
11. Had pulmonary function tests (PFTs) within 90 days prior to Day 1 with total lung capacity ≥ 65% (predicted);
12. Had a ventilation-perfusion (V/Q) lung scan, spiral/helical/electron beam computed tomography (CT), or pulmonary angiogram prior to Day 1 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 pulmonary hypertension;
13. Has adequate kidney function defined as an estimated glomerular filtration rate (eGFR) ≥ 45 mL/min/1.73 m^2 as measured by the central lab;
14. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures;
15. 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.

Major exclusion criteria:

1. Participation in other investigational clinical studies involving interventional 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 90 days prior to Day 1 or planned initiation during the study;
3. Stopped receiving any PAH chronic therapy within 60 days prior to Day 1;
4. Received a dose of prednisone > 20 mg/day (or equivalent dose if other corticosteroid) within 30 days prior to Day 1;
5. Received intravenous (iv) or subcutaneous (sc) prostacyclin/prostacyclin analogues within 90 days prior to Day 1;

6. Received intravenous inotropes within 30 days prior to Day 1;
7. Has uncontrolled systemic hypertension as evidenced by sitting systolic blood pressure (BP) > 160 mm Hg or sitting diastolic BP > 100 mm Hg during Screening after a period of rest;
8. Has systolic BP < 90 mm Hg during Screening after a period of rest;
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 90 days of Day 1;
    e. Symptomatic coronary artery disease within the last 3 years;
10. Acutely decompensated heart failure within 30 days prior to Day 1, per investigator assessment;
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. Uncontrolled obstructive sleep apnea;
14. 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);
15. Serum aminotransferase (ALT or AST) levels > 1.5X the upper limit of normal (ULN) at Screening;
16. Hemoglobin (Hgb) concentration < 10.5 g/dL at Screening;
17. Diagnosis of Down syndrome;
18. History of malignancy within 5 years prior to Screening, with the exception of localized skin or cervical carcinomas;
19. Untreated or uncontrolled active bacterial, fungal, or viral infection;
20. Known or suspected active drug or alcohol abuse, per investigator judgment;

21. Use of inhaled nitric oxide within 7 days prior to Screening and Day 1 visits, excluding acute vasodilator testing during diagnostic cardiac catheterization;
22. Major surgery within 30 days prior to Day 1 or planned to occur during the course of the study;
23. Unwilling to practice acceptable 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 because of language problems, poor mental development, or impaired cerebral function.
30. Patient has active myositis;
31. Use of total parenteral nutrition within one year of the Day 1 study visit;
32. History of acute renal crisis within one year of the Day 1 study visit;
33. Patient has participated in investigational trials where bardoxolone methyl was administered.

Investigational product, dosage and mode of administration:
Bardoxolone methyl will be administered orally once a day at 2.5, 5, or 10 mg.

Duration of treatment:
Bardoxolone methyl or placebo will be administered once a day for 24 weeks.

Reference therapy, dosage and mode of administration:
Placebo will be administered orally once a day for 24 weeks.

Criteria for evaluation:
Efficacy: 6MWD, clinical improvement composite events[redacted]
Safety: Results of physical examinations, laboratory results (clinical chemistry, hematology, urinalysis), vital sign measurements, ECG results, weight, adverse events, and serious adverse events.
[redacted]
Pharmacokinetics: Bardoxolone methyl plasma concentration-time data, and estimated pharmacokinetic parameters for each analyte.

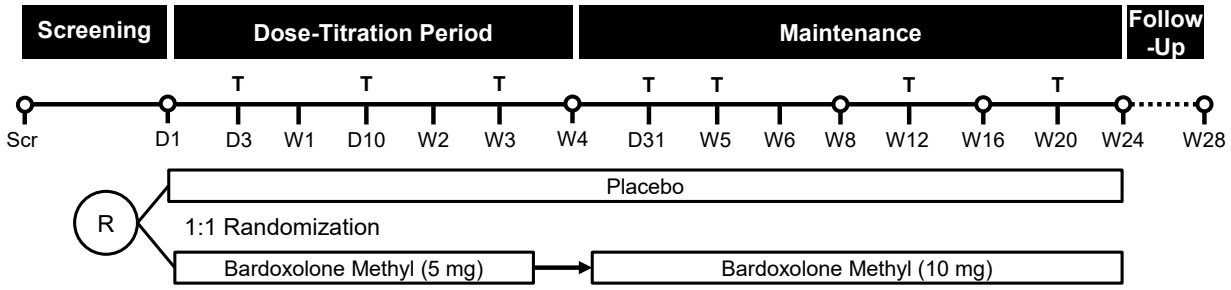
Statistical methods:
[redacted]

[redacted]

Primary analysis of efficacy: A mixed-model repeated measures (MMRM) analysis will compare the treatment groups with respect to the primary endpoint. The dependent variable will be change from baseline in 6MWD. The model will include treatment, visit, and the treatment-by-visit interactions as fixed effects; stratification by number of background PAH therapies (0, 1, or 2); and visit as a repeated measure having an unstructured covariance structure. Covariates may be defined in the statistical analysis plan as appropriate. Missing data will not be imputed for the primary analysis.

[redacted]

Schema for Study of Bardoxolone Methyl in Patients with CTD-PAH



o 6-Minute Walk Test
T Telephone Contact

Patients who complete the study and are treatment-compliant to their assigned dose will be eligible for a separate open-label extension study.

3. TABLE OF CONTENTS AND LIST OF TABLES

TABLE OF CONTENTS

LIST OF TABLES

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
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
ATP	Adenosine triphosphate
ATS	American Thoracic Society
AUC	Area under the concentration-time curve
BMI	Body mass index
BNP	B-type natriuretic peptide
BP	Blood Pressure
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations (US)
CK	Creatine kinase
CKD	Chronic kidney disease
C_{max}	Maximum drug concentration in plasma
CT	Computed tomography
CTD	Connective tissue disease
CTD-PAH	Connective tissue disease-associated pulmonary arterial hypertension

Abbreviation or Specialist Term	Explanation
CTEPH	Chronic thromboembolic pulmonary hypertension
[redacted]	[redacted]
DSMB	Data safety monitoring board
EC	Ethics Committee
eCRF	Electronic case report form
ECG	Electrocardiogram
ECHO	Echocardiogram
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ERA	Endothelin receptor antagonist
$FADH_2$	Flavin adenine dinucleotide
FDA	Food and Drug Administration (US)
FEV_1	Forced expiratory volume
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
HCV	Hepatitis C virus
HDPE	High-density polyethylene
Hgb	Hemoglobin
ICH	International Conference on Harmonization
IKKβ	Inhibitor of nuclear factor kappa β kinase beta subunit
INR	International normalized ratio
IRB	Institutional Review Board
IWRS	Interactive Web Response System
ITT	Intent-to-treat
Keap1	Kelch-like ECH associated protein-1
LDH	Lactate dehydrogenase
MAR	Missing at random
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MMRM	Mixed model repeated measures

Abbreviation or Specialist Term	Explanation
MRI	Magnetic resonance imaging
NADH	Nicotinamide adenine dinucleotide
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B-cells
Nrf2	Nuclear factor (erythroid-derived 2)-related factor 2
NT-Pro BNP	N-Terminal Pro-Brain Natriuretic Peptide
NYHA FC	New York Heart Association Functional Classification
PAH	Pulmonary arterial hypertension
PCWP	Pulmonary capillary wedge pressure
PEF	Peak expiratory flow
PFT	Pulmonary function test
PH	Pulmonary hypertension
PK	Pharmacokinetic
RBC	Red blood cell
RHC	Right heart catheterization
ROS	Reactive oxygen species
SAE	Serious adverse event
SAP	Statistical analysis plan
[redacted]	[redacted]
SLE	Systemic lupus erythematosus
SRC	Sample size re-calculation committee
TBL	Total bilirubin
TLC	Total lung capacity
T_{max}	Time when maximum drug concentration in plasma is achieved
TV	Tidal volume
ULN	Upper limit of normal
US	United States
V/Q	Ventilation-perfusion
WBC	White blood cell
WHO	World Health Organization
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 Nrf2 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. Activation of the Nrf2 pathway also transcriptionally regulates multiple genes that promote the production of cellular energy within the mitochondria and facilitates mitochondrial homeostasis and efficiency.

Through induction of Nrf2 and suppression of NF-κB, bardoxolone methyl has broad molecular and pharmacological effects that address multiple facets of the pathophysiology of PAH. Induction of NF-κB is markedly elevated in macrophages, endothelial cells and smooth muscle cells of PAH patients (Price, 2010). Recent evidence demonstrates that genetic or pharmacologic induction of Nrf2 suppresses formation of the PAH 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 systemic metabolic and skeletal muscle dysfunction as a major cause of reduced functional capacity and fatigue, as well as disease progression. A high frequency of insulin resistance and metabolic syndrome-like features have been described in patients with PAH, and glucose intolerance is associated with a decrease in 6MWD (Pugh, 2011). Pulmonary hypertension patients have decreased ATP production (Sutendra, 2014), which results in skeletal muscle dysfunction and impaired functional 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).

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. Since Nrf2 activation can increase mitochondrial respiration (Holmström, 2013; Ludtmann, 2014), bardoxolone methyl may restore metabolic deficits in PAH, thereby acutely improving energy production and 6MWD.

Common connective tissue diseases (CTD) associated with PAH (CTD-PAH) include autoimmune diseases such as scleroderma, systemic lupus erythematosus (SLE), and mixed

CTD. Nrf2 is a gene that determines susceptibility to autoimmune disease, and genetic deletion of Nrf2 results in the spontaneous development of lupus-like autoimmune nephritis (Yoh, 2001) and systemic autoimmune disease (Li, 2004) in mice. An autoimmune mechanism associated with vascular endothelial damage appears to play a key pathogenic role in the development of PAH in these patients. Preclinical data demonstrate that bardoxolone methyl and analogs are therapeutically effective in autoimmune disease models by significantly reducing auto-antibody levels, disease burden, and improving survival (Wu, 2014; Wei, 2014). Thus, in addition to the aforementioned anti-inflammatory and bioenergetics effects, bardoxolone methyl targets autoimmune-associated inflammation, which likely causes bioenergetics and other deficits in CTD-PAH patients.

Despite available therapies, the prognosis for PAH remains poor, especially for patients with connective tissue disease (Chung, 2014). Approved vasodilation therapies generally do not yield significant functional improvements in CTD-PAH patients (Ghofrani, 2013; Tapson, 2013). Notably, none of the approved therapies target the metabolic and mitochondrial dysfunction. [redacted] Thus, bardoxolone methyl may provide a novel approach to PAH therapy through improvements in bioenergetics and mitochondrial function that translate to increased muscular function and exercise capacity, especially in CTD-PAH patients who do not respond well to vasodilator treatment.

Preliminary efficacy data from a Phase 2 study in World Health Organization (WHO) Group I PAH patients with bardoxolone methyl (402-C-1302, LARIAT, NCT02036970) showed that bardoxolone methyl improves 6MWD on top of optimal vasodilation background therapies in CTD-PAH patients. These observed benefits may reflect bardoxolone methyl's novel anti-inflammatory and mitochondrial effects, as well as the attenuation of autoimmune processes that likely contribute to PAH in patients with connective tissue diseases.

Thus, the established pharmacologic effects of bardoxolone methyl, including the suppression of pathologic NF-κB signaling and inflammation, mitochondrial dysfunction, and autoimmune processes, are directly applicable to the treatment of WHO Group I CTD-PAH. Given the nonclinical and clinical evidence supporting potential efficacy of bardoxolone methyl in CTD-PAH, the Sponsor proposes a clinical study to test bardoxolone methyl in patients with CTD-PAH.

5.1. Clinical Experience with Bardoxolone Methyl

Approximately 1900 individuals have been exposed to bardoxolone methyl. Sixteen studies have been completed (seven in patients with CKD who also had type 2 diabetes, four in non-CKD indications, and five in healthy subjects) and one study is ongoing in patients with PH.

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, oncology, CKD, and PH patients with bardoxolone methyl.

5.1.2. Fluid Overload

Similar to endothelin receptor antagonists (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 conducted mostly in patients with Stage 3b CKD (eGFR of 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.

In a Phase 2 dose-ranging study of the efficacy and safety of bardoxolone methyl in patients with pulmonary hypertension (LARIAT), risk mitigation procedures were employed to reduce the potential for bardoxolone methyl-induced fluid overload; these procedures excluded patients with the identified risk factors and ensured close monitoring for fluid retention within the first month of treatment. To date, the risk for acute fluid overload adverse events with bardoxolone methyl in late-stage CKD patients has not been observed in PAH patients.

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. These increases were not 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; they peak approximately two to four weeks later. In most patients, transaminase elevations were mild, but approximately 4% to 11% of patients experienced an elevation greater than 3X 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 3X the ULN sometimes required additional time to resolve. While some patients have had elevations to above 3X the ULN, persistent elevations to above 3X 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 who also had 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 have also been reported in bardoxolone methyl-treated PAH patients but at lower incidences than that observed in prior CKD studies. Moreover, the incidence of muscle spasms is similar to that observed in placebo-treated PAH patients. 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 defined subset of patients enrolled in a Phase 2a study. To date, in those cases where serum creatinine kinase (CK) levels have been measured, no association has been observed between muscle spasms and elevated CK 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.

Increases in the whole-body glucose disposal rate have been 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).

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 who also had type 2 diabetes. In studies of these patients, 17% of bardoxolone methyl patients reported 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 weight (in absolute terms) than those of normal or moderately-elevated body-mass index.

Bardoxolone methyl-treated PAH patients have also had decreases in weight, with mean weight decreases of approximately 3 kg versus placebo at Week 16. Weight loss in PAH patients has not coincided with reports of decreased appetite or anorexia adverse events.

5.1.6. Hypomagnesaemia

Hypomagnesaemia has not been reported in PAH patients to date, but was reported as an adverse event for 15.5% of patients with CKD who also had type 2 diabetes who received bardoxolone

methyl. The adverse event of hypomagnesaemia (of any reported relationship to study drug) 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 showed no 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, a thorough QT study that tested doses of bardoxolone methyl up to 80 mg, bardoxolone methyl showed no increase in the QT interval.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

For patients with connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) enrolled in this study, the objectives are as follows:

6.1.1. Primary Objective

To assess the efficacy of bardoxolone methyl relative to placebo.

6.1.2. Secondary Objective

To assess the safety of bardoxolone methyl relative to placebo.

6.2. Endpoints

6.2.1. Primary Efficacy Endpoint

Change from baseline in six-minute-walk distance (6MWD) relative to placebo at Week 24

6.2.2. Secondary Efficacy Endpoints

Time-to-first clinical improvement event consisting of a persistent change for any of the following:

- Improvement by at least one WHO functional class
- Increase from baseline in 6MWD by at least 10%
- Decrease from baseline in creatine kinase (as a surrogate biomarker for muscle injury and inflammation) by at least 10%

The persistence of the change in WHO functional class, 6MWD, or creatinine kinase must be confirmed by a successive assessment also meeting the defined criteria. The confirmatory assessment must be at least 14 days after the initial assessment, or at the next scheduled assessment.

[redacted]

[redacted]

6.2.4. Safety Endpoints

Frequency, intensity, and relationship to study drug of adverse events and serious adverse events, and change from baseline in the following assessments: physical examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), clinical laboratory measurements, and weight.

[redacted]

6.2.6. Pharmacokinetic Endpoints

Systemic exposure to bardoxolone methyl will be assessed in all patients. Additional blood sampling will be performed in a subset of patients for the purpose of obtaining more robust pharmacokinetic (PK) parameter estimates (*e.g.*, AUC, C_{max}, T_{max}) for bardoxolone methyl in the CTD-PAH population.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This double-blind, randomized, placebo-controlled trial will study the safety, tolerability, and efficacy of bardoxolone methyl in qualified patients with WHO Group I CTD-PAH.

Qualified patients will be randomized 1:1 to either bardoxolone methyl or placebo to be administered once daily for 24 weeks. Patients randomized to placebo will remain on placebo throughout the study and undergo sham titration. Patients randomized to bardoxolone methyl will start at 5 mg and will dose-escalate to 10 mg at Week 4, unless contraindicated clinically. Dose de-escalation is permitted during the study if indicated clinically. Please refer to Section 7.3.1 for additional details on dose escalation and dose de-escalation.

All patients in the study will follow the same visit and assessment schedule. Following randomization, patients will be scheduled to be assessed in person during treatment at Weeks 1, 2, 4, 6, 8, 16, and 24 and by telephone contact on Days 3, 10, 21, 31, 38, 84, and 140. Patients will also be scheduled to be assessed at an in-person follow up visit at Week 28, four weeks after the end of treatment.

Patients who complete the study and are treatment-compliant to their assigned dose will be eligible for a separate open-label extension study.

7.1.1. Blinded Sample Size Re-Calculation

A sample size re-calculation will be performed to evaluate on a blinded basis the study assumptions used to calculate sample size. A sample size re-calculation committee (SRC), comprised of Sponsor personnel and the study's blinded statistician, will be established to re-calculate sample size based on blinded assessment of study assumptions. The SRC will review available data (*e.g.*, baseline characteristics, study drug discontinuations, variability in 6MWD change from baseline, intra-patient autocorrelations of 6MWD) when approximately 100 patients have been enrolled in the study. The Sponsor may increase the sample size of the study up to approximately 200 patients. An increase of sample size within this range will be documented in a note-to-file to the investigators/IRBs/ECs (as appropriate) and will not require a protocol amendment. Because these analyses will be based on pooled, blinded data they will not impact the Type I error rate. An appendix to the Statistical Analysis Plan (SAP) will present details regarding the planned re-calculation of sample size.

7.2. Number of Patients

Approximately 130 patients will be enrolled; this number may be increased up to approximately 200 patients based upon a blinded sample size re-calculation.

7.3. Treatment Assignment

Qualified patients will be randomized 1:1 to either bardoxolone methyl or placebo to be administered once daily for 24 weeks. Randomization will be performed using an interactive

web response system (IWRS). Patients randomized to placebo will remain on placebo throughout the study, but will follow sham titration to maintain the blind.

7.3.1. Dose Escalation and Dose De-Escalation

Patients randomized to bardoxolone methyl will start at 5 mg and will dose-escalate to 10 mg at Week 4, unless contraindicated clinically. The investigator should discuss any reason for not dose-escalating at Week 4 with the medical monitor. The investigator may choose to decrease the patient's dose to one-half of the prior dose (*e.g.*, 10 mg to 5 mg) if clinically indicated. Dose de-escalation can occur more than once, but the minimum dose permitted is 2.5 mg. Reasons for dose de-escalation should be discussed with the medical monitor prior to changing dose.

The Week 4 visit is the only study visit when dose escalation is permitted. Patients may have 1 dose de-escalation prior to Week 4. At Week 4, all patients should dose escalate, unless contra-indicated and discussed with the medical monitor.

If patients did not dose de-escalate prior to Week 4, then:

- If patients dose escalate at Week 4, at most 2 dose de-escalations are permitted after Week 4
- If patients did not dose escalate at Week 4, then only 1 dose de-escalation is permitted after Week 4

If patients did dose de-escalate prior to Week 4, then:

- If patients did dose escalate at Week 4, only 1 dose de-escalation is permitted after Week 4
- If patients did not dose escalate at Week 4, then no further dose de-escalations are permitted after Week 4

After Week 4, once a patient's dose has been reduced, dose escalation back to a higher dose is not permitted. If a patient's dose was reduced to 2.5 mg prior to the Week 4 visit, they are permitted to escalate to 5 mg at Week 4.

Unscheduled visits due to dose de-escalation should include assessments detailed in Section 9.7.

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 drug 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 lists the overall schedule of assessments for the study.

Table 3: Schedule of Assessments

Assessment \ Study Week (Day)	Screen A[a]	Screen B[b]	Day 1[c]	Week 1 (Phone) Day 3±2	Week 1 Day 7±3	Week 2 (Phone) Day 10±2	Week 2 Day 14±3	Week 3 (Phone) Day 21±2	Week 4 Day 28±3	Week 4 (Phone) Day 31±2	Week 5 (Phone) Day 38±2	Week 6 Day 42±3
Informed consent	X											
Inclusion/ exclusion	X		X[d]									
Demographics and baseline disease characteristics	X											
Prior and Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Current PAH background medications	X	X	X	X	X	X	X	X	X	X	X	X
Medical history	X											
Height	X											
Echocardiogram[e]	X											
Weight at home			X	X	X	X	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	X	X
Weight in clinic	X		X		X		X		X			X
ECG	X											
Vital sign measurements	X	X	X		X		X		X			X
Physical exam[f]	X		X		X		X		X			X
Pulmonary function testing	X[g]											
[redacted]			X									
Right heart catheterization	X[i]											
V/Q scan[j]	X											
Pregnancy test for WOCBP[k]	X	X	X						X			
Study drug administration			X	---------- X ----------								
Dispense study drug			X						X			
Collect study drug									X			
Telephone contact				X		X		X		X	X	
Adverse event collection			X[l]	X	X	X	X	X	X	X	X	X
Clinical chemistry	X	X	X		X		X		X			X
BNP and NT-Pro BNP	X	X	X		X		X		X			X
Hematology	X	X	X		X		X		X			X
Urinalysis and microscopy	X		X		X		X		X			X
Virus serology	X											
6-min walk test	X	X	X						X			
[redacted]	X	X	X						X			
[redacted]			X[n]		X[o]							
[redacted]			X									
WHO functional class[p]	X		X		X		X		X			X
[redacted]	X											
[redacted]	X		X									
PK samples[r]												

Study Week (Day) / Assessment	Week 8 Day 56±3	Week 12 (Phone) Day 84±2	Week 16 Day 112±3	Week 20 (Phone) Day 140±2	Week 24 (1) or Week 24 Day Prior Visit[u] Day 167±3	Week 24 (2) or End of Treatment Visit[v] Day 168±3	Week 28 Follow-up[v] Day 196±3
Informed consent							
Inclusion/ exclusion							
Demographics and baseline disease characteristics							
Concomitant medications	X	X	X	X		X	X
PAH medications	X	X	X	X		X	X
Medical history							
Height							
Echocardiogram[e]							
Weight at home	X	X	X	X		X	
Dispense weight diary	X		X			X	
Collect/review weight diary	X		X			X	
Weight in clinic	X		X			X	X
ECG						X	X
Vital sign measurements	X		X			X	X
Physical exam[f]	X		X			X	X
Pulmonary function testing	X		X			X	
[redacted]	X		X			X	
Right heart catheterization							
V/Q scan[j]							
Pregnancy test for WOCBP[k]	X		X			X	X
Study drug administration	---------- X ----------						
Dispense study drug	X		X				
Collect study drug	X		X			X	
Telephone contact		X		X			
Adverse event collection	X	X	X	X		X	X
Clinical chemistry	X		X			X	X
BNP and NT-Pro BNP	X		X			X	X
Hematology	X		X			X	X
Urinalysis and microscopy	X		X			X	X
Virus serology							
6-min walk test	X		X		X[u]	X[u]	X
[redacted]	X		X		X	X	X
[redacted]			X[n]			X[o]	
[redacted]						X	
WHO functional class[p]	X		X			X	X
[redacted]	X		X			X	
[redacted]	X		X			X	
PK samples[r]	X[s]				X[s,t]	X[t]	

[a] Total Screening period should not exceed 90 days.

[b] Screen B is only required for patients if the Day 1 visit is more than 28 days after the Screen A visit.

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

[d] Screening 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.

[e] If an echocardiogram has not been performed within 90 days of Day 1, echocardiogram must be performed during Screening to confirm left ventricular ejection fraction ≥ 40%.

[f] [redacted].

[g] Pulmonary function tests within 90 days prior to Day 1 may be used to determine eligibility.

[h] [redacted]

[i] Right heart catheterization within 36 months prior to Day 1 may be used to determine eligibility.

[j] Patients who have not had a V/Q scan, spiral/helical/electron beam computed tomography (CT), or pulmonary angiogram prior to Screening should have this assessment performed to determine eligibility. If V/Q scan is abnormal at Screening (*i.e.*, results other than normal or low probability), then a confirmatory CT or selective pulmonary angiography must also be performed at Screening to exclude chronic thromboembolic pulmonary hypertension (CTEPH).

[k] A serum pregnancy test will be performed at the Screening visit 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 if requested by a local health authority or IRB/EC. For WOCBP enrolled in the UK and Argentina, pregnancy testing will be performed every 4 weeks while taking study drug.

[l] AE assessments on Day 1 should be performed following study drug administration.

[m] [redacted]

[n] [redacted]

[o] [redacted]

[p] [redacted]

[q] [redacted]

[r] Patients must be instructed to not take their study drug prior to coming to the clinic for visits when PK samples will be collected. Patients must administer the study drug dose in the clinic on PK sample collection visits after the 0 hour PK blood sample is collected. Patients will have blood samples for PK analysis drawn just prior to (0 hour) and after (2 and 4 hours) dose administration.

[s] Patients participating in the PK sub-study will have 5 additional blood samples for PK analysis drawn for this visit. PK sub-study patients will have blood samples for PK analysis drawn just prior to (0 hour) and after (1, 2, 3, 4, 6, 8, and 24 hours) dose administration for this visit.

[t] Patients not participating in the PK sub-study may have blood collected on either day of the Week 24 visit.

[u] The 6-minute walk test must be performed on two separate days within the 3-day window at Week 24.

[v] Patients who terminate from the study prior to the Week 24 study visit should be brought back to the clinic as soon as possible for early termination assessments (*i.e.*, Week 24 Day Prior and end-of-treatment visits) as well as a follow-up visit 4 weeks later. Patients should complete the end-of-treatment procedures, including the 6MWT, prior to any adjustments being made to their PAH treatment regimen.

Abbreviations: ECG = electrocardiogram, PK = pharmacokinetic, V/Q = ventilation-perfusion, WOCBP = women of child-bearing potential, 6MWT = 6-minute walk test, [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/NYHA FC class II and III;
4. WHO Group I PAH associated with connective tissue disease;
5. Had a diagnostic right heart catheterization performed and documented within 36 months prior to Day 1 that confirmed a diagnosis of PAH according to all the following criteria:
    a. Mean pulmonary artery pressure ≥ 25 mm Hg (at rest);
    b. Pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg;
    c. Pulmonary vascular resistance > 240 dyn•sec/cm^5 or > 3 mm Hg/liter (L)/minute;
6. Has BNP level ≤ 400 pg/mL;
7. Had an average 6MWD ≥ 150 meters on two consecutive tests performed on different days prior to randomization, with a percent difference ≤ 15% between tests;
8. Has been receiving no more than two (2) approved disease-specific PAH therapies. PAH therapy must have been at a stable dose for at least 90 days prior to Day 1. No additions or changes should be made to PAH therapies and doses should remain stable for the duration of the study;
9. Has maintained a stable dose for 30 days prior to Day 1 if receiving therapies that may affect walking distance, including but not limited to: vasodilators (including calcium channel blockers), digoxin, L-arginine supplementation, oxygen supplementation, diuretics, agents to treat neuropathic pain associated with peripheral neuropathy (such as pregabalin), and/or agents to treat anemia (such as 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;
10. If receiving treatment for CTD with prednisone or any other drugs, the medications must remain the same for at least 90 days prior to Day 1. Doses for medications prescribed for the treatment of CTD must remain stable for at least 30 days prior to Day 1 and for the duration of the study;
11. Had pulmonary function tests (PFTs) within 90 days prior to Day 1 with total lung capacity ≥ 65% (predicted);
12. Had a ventilation-perfusion (V/Q) lung scan, spiral/helical/electron beam computed tomography (CT), or pulmonary angiogram prior to Day 1 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 pulmonary hypertension;

13. Has adequate kidney function defined as an estimated glomerular filtration rate (eGFR) $\geq$ 45 mL/min/1.73 m^2 as measured by the central lab;
14. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures;
15. 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.

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 interventional 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 90 days prior to Day 1 or planned initiation during the study;
3. Stopped receiving any PAH chronic therapy within 60 days prior to Day 1;
4. Received a dose of prednisone >20 mg/day (or equivalent dose if other corticosteroid) within 30 days prior to Day 1;
5. Received intravenous (iv) or subcutaneous (sc) prostacyclin/prostacyclin analogues within 90 days prior to Day 1;
6. Received intravenous inotropes within 30 days prior to Day 1;
7. Has uncontrolled systemic hypertension as evidenced by sitting systolic blood pressure (BP) > 160 mm Hg or sitting diastolic BP > 100 mm Hg during Screening after a period of rest;
8. Has systolic BP < 90 mm Hg during Screening after a period of rest;
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 90 days of Day 1;
    e. Symptomatic coronary artery disease within the last 3 years;

10. Acutely decompensated heart failure within 30 days prior to Day 1, per investigator assessment;
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. Uncontrolled obstructive sleep apnea;
14. 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);
15. Serum aminotransferase (ALT or AST) levels > 1.5X the upper limit of normal (ULN) at Screening;
16. Hemoglobin (Hgb) concentration < 10.5 g/dL at Screening;
17. Diagnosis of Down syndrome;
18. History of malignancy within 5 years prior to Screening, with the exception of localized skin or cervical carcinomas;
19. Untreated or uncontrolled active bacterial, fungal, or viral infection;
20. Known or suspected active drug or alcohol abuse, per investigator judgment;
21. Use of inhaled nitric oxide within 7 days prior to Screening and Day 1 visits, excluding acute vasodilator testing during diagnostic cardiac catheterization;
22. Major surgery within 30 days prior to Day 1 or planned to occur during the course of the study;
23. Unwilling to practice acceptable 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 because of language problems, poor mental development, or impaired cerebral function.
30. Patient has active myositis;
31. Use of total parenteral nutrition within one year of the Day 1 study visit;
32. History of acute renal crisis within one year of the Day 1 study visit;
33. Patient has participated in investigational trials where bardoxolone methyl was administered.

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 Discontinuation and Termination

Patients have the right to discontinue study drug or withdraw from the study at any time for any reason, without prejudice to their medical care. Furthermore, the investigator may discontinue a patient from study drug. Consultation with the medical monitor should occur prior to study drug discontinuation or withdrawing a patient from the study. The reason for a patient's discontinuation from study drug or study termination will be recorded in the electronic case report form (eCRF).

8.4.1. Patient Discontinuation Criteria

Discontinuation refers to a patient's stopping administration of study drug. Reasons for study drug discontinuation may include the following:

- Confirmed clinical worsening event
- Occurrence of an AE or change in medical status that leads the investigator to be concerned about the patient's welfare
- Administrative reasons (*e.g.*, inability to continue)
- Sponsor termination of the study
- Voluntary withdrawal
- Females who become pregnant during the study
- Investigator unblinding

Patients must discontinue study drug 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%);

Patients who are discontinued from study drug should still continue in the study, completing all study visits and undergo all scheduled study assessments, if possible.

8.4.2. Patient Termination Criteria

Termination refers to a patient's stopping study drug and all study assessments and visits. Reasons for study termination include the following:

- Loss to follow-up
- Death
- Withdrawal of consent

Every reasonable 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, request the patient return for end-of-treatment and follow-up visits (if applicable), and follow up with the patient regarding any unresolved AEs.

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 8 weeks 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 the first 8 weeks of the study 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 who experience a five pound (2.3 kilogram) or greater increase in weight between Day 1 and Week 8 may not restart their study medication until the investigator has completed and documented an assessment of fluid overload.

Patients who experience a five pound (2.3 kilogram) or greater increase in weight after the Week 8 study visit will be instructed return to the clinic for an unscheduled physical examination and laboratory assessment by the investigator. Study medication should not be discontinued unless the investigator has completed and documented an assessment of fluid overload and determines that the patient should be discontinued.

Investigators should 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, 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.

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 to 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 3X the ULN for at least one week or until 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 > 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%);

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

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 a patient experiences 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.

Patients with anemia who re-screen must repeat all Screening assessments at the re-screening. If the patient takes agents to treat anemia (including but not limited to supplemental iron, erythropoietin, or intravenous iron) the patient must remain on a stable dosage for at least 30 days prior to Day 1. If the patient receives intravenous iron therapy during Screening, the intravenous infusion must be performed at least 30 days prior to Day 1.

9.2. Description of Study Drug

Bardoxolone methyl (RTA 402) drug product information is shown in Table 4. Information about the placebo is shown in Table 5.

Table 4: Bardoxolone Methyl Drug Product Information

Description	Bardoxolone methyl capsule (2.5 mg, 5 mg)
[redacted]	[redacted]
Route of Administration	Oral

Table 5: Placebo Information

Description	Placebo for bardoxolone methyl capsule (2.5 mg, 5 mg)
Ingredients	Silicified Microcrystalline Cellulose Lactose monohydrate Magnesium Stearate Gelatin capsules Titanium Dioxide (capsule pigment)
Route of Administration	Oral

9.3. Concomitant Medications

9.3.1. Excluded Medications

Patients taking these medications or treatments will be ineligible for enrollment:

- Any other investigational drug or device as part of an interventional study;

- Intravenous or subcutaneous prostacyclin/prostacyclin analogue;
- Intravenous inotropes;
- Inhaled nitric oxide (excluding acute vasodilator testing during diagnostic cardiac catheterization);
- Prednisone at a dosage > 20 mg/day within 30 days prior to Day 1 or at any time during the study;

Patients who take excluded medications during the study should not discontinue study drug solely on this basis. Consultation with the medical monitor should occur prior to study drug discontinuation or withdrawing a patient from the study.

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;
- Oral, implantable, or injectable contraceptives.

Patients taking medication chronically should be maintained on those same doses and dose schedules throughout the study period and should not have additions or changes made to their medications, as medically feasible.

The use of the following therapies, which may affect walking distance, 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 and discussed with the medical monitor, 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.

If receiving treatment for CTD with prednisone or any other drugs, the medications must remain the same for at least 90 days prior to Day 1. Doses for medications prescribed for the treatment

of CTD must remain stable for at least 30 days prior to Day 1 and 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.

Refer to Section 9.10.26 for guidelines on oxygen use during 6MWTs. Initiation of supplemental long-term oxygen therapy (oxygen application for more than 30 consecutive days) or persistent modification of a pre-existing supplemental long-term oxygen therapy (*i.e.*, need for a persistent increase of the amount of delivered oxygen for more than 30 days) due to worsening PAH is permitted.

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

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. Patients who miss more than 42 doses (*i.e.*, 25% of the 168 expected doses) will not be considered treatment-compliant. Patients must be considered treatment-compliant to be eligible for the open-label extension study.

9.5. Randomization

An IWRS will be utilized to randomize patients 1:1 to bardoxolone methyl or placebo. Randomization will be stratified by number of background PAH therapies: 0, 1, or 2.

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. To prevent potential bias, appropriate measures will be taken to ensure the blind is maintained for the patients and personnel mentioned previously. To maintain the blind, investigators will distribute blinded study drug treatment kits to patients as directed by the IWRS system. Investigators and patients will not be blinded to dose level, but will be blinded to treatment assignment (*i.e.*, active study drug vs. placebo).

An IWRS system will manage treatment assignments. The only people with direct access to treatment assignments will be those individuals who develop and maintain the randomization code, the DSMB and the statistical group reporting to the DSMB.

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 strongly encouraged to contact the medical monitor to discuss situations in which he or she believes that the blind should be broken, but ultimately 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, the investigator must describe the event that required unblinding 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 study drug discontinuation 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, regulatory agencies) must be provided with unblinded information according to the applicable regulatory requirement. This information must not be conveyed to any 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. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will review unblinded safety data throughout the study and make recommendations as appropriate. The DSMB will begin quarterly data reviews approximately 3 months after the first patient is enrolled and continue through the last dose of the last patient enrolled.

The DSMB will consist of external experts supported by an independent statistical group. The independent statistical group will prepare unblinded analyses for the DSMB and will not have a role in the statistical analysis plan (SAP) after the study has started enrolling patients. A separate, blinded statistical group (*i.e.*, not associated with the DSMB) will be responsible for producing and finalizing the SAP and executing final data analysis of the study.

The DSMB will be governed by a charter that will describe the following:

- Roles and responsibilities of the DSMB members and the independent statistical group
- Meeting format and frequency
- Communication channels between the DSMB, the independent statistical group, the Sponsor, and the blinded study statisticians
- Voting process and requirements (*e.g.*, requirement of consensus for issuance of a termination recommendation)
- Provisions governing conflict of interest and confidentiality
- Process for interim analysis of efficacy, including the alpha spending function

Briefly, the DSMB will review the progress of the study and the accumulating unblinded data while the study is ongoing. The DSMB will make recommendations to Sponsor representatives following each meeting. The DSMB may recommend that the study continue as is, be modified to protect patient safety, or be terminated. However, investigators, and not the DSMB, will make intra-patient dose-escalation decisions at the Week 4 visit for each patient and may choose to decrease the patient's dose (to one-half of the prior dose).

9.7. Unscheduled Visits

Unscheduled visits are allowed for the following reasons:

- Assessment of weight gain 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;
- Any time the investigator feels that it is clinically appropriate for patient safety.

At a minimum, unscheduled visits should include collection of adverse events, clinical chemistry, hematology, concomitant medications and vital signs, as well as collection/review of weight diary. Additional conversations may be necessary with the medical monitor following an unscheduled visit to assess patient safety.

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 acceptable 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 the serum pregnancy test confirms the pregnancy, 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 to manage tolerability issues. Dose escalations are not permitted beyond the scheduled Week 4 visit. Once a patient's dose has been reduced, that dose should be maintained until the Week 24 visit. Patients who resume therapy after an interruption will follow the originally planned study schedule.

9.10. Study Procedures

The following sections describe each assessment. The timing of these assessments is noted in Table 3. 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 must be reviewed as indicated in Table 3. 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 as indicated in Table 3. Baseline disease characteristics will be collected as indicated in Table 3.

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 as indicated in Table 3 and all changes will be recorded.

9.10.5. Current PAH Background Medications

The name, dose, and frequency must be recorded for all PAH background medications that the patient is taking. PAH background medications are those that have been approved by the FDA or the local health authority for the treatment of PAH. Trade or generic drug names should be used where possible. PAH background medications will be reviewed as indicated in Table 3 and all changes will be recorded. Additional background PAH medications may only be prescribed after a clinical worsening event is confirmed.

9.10.6. 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 as indicated in Table 3.

9.10.7. Height

Height should be measured without footwear or prosthetics as indicated in Table 3.

9.10.8. Echocardiogram

If an echocardiogram has not been performed within 90 days of Day 1, an echocardiogram must be performed during Screening to confirm eligibility as indicated in Table 3.

9.10.9. Weight and Body Mass Index (BMI)

Weight must be measured as indicated in Table 3. 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 measure weight, and a diary will be provided to record the at-home weight measurements and the self-administration of study drug. Weights recorded in patient diaries will not be entered in the eCRF. Weights should be taken at the same time each day and recorded in a patient diary. During the first eight weeks, weights will be recorded daily; weekly weights will be recorded thereafter. Patients will be instructed to stop administering study drug and contact the investigator if their daily weight increases 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.

9.10.10. Electrocardiograms (ECG)

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

9.10.11. Vital Sign Measurements

Vital sign measurements include the patient's heart rate (beats/minute taken for at least 15 seconds), respiration rate, and 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 as indicated in Table 3.

9.10.12. Physical Examination

A comprehensive physical examination must be performed by a physician, physician assistant, or registered nurse practitioner as indicated in Table 3 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; 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. Pulmonary Function Testing [redacted]

Pulmonary function testing that includes forced vital capacity (FVC), FVC percent predicted (FVC%), forced expiratory volume in 1 second (FEV1), FEV1 percent predicted (FEV1%), FEV1/FVC ratio, peak expiratory flow (PEF), and total lung capacity (TLC), must be performed as indicated in Table 3.

[redacted]

9.10.14. Ventilation-Perfusion (V/Q) Lung Scan, Spiral/Helical/Electron Beam Computed Tomography (CT) or Pulmonary Angiogram

Ventilation-perfusion (V/Q) lung scan, spiral/helical/electron beam computed tomography (CT) or pulmonary angiogram are required to determine eligibility. If this assessment has not been previously performed for a patient, it must be performed at Screening. If V/Q scan is abnormal at Screening (*i.e.*, results other than normal or low probability), then a confirmatory CT or selective pulmonary angiography must be performed at Screening to exclude chronic thromboembolic pulmonary hypertension (CTEPH).

9.10.15. Right Heart Catheterization

A right heart catheterization (RHC) completed within 36 months of Day 1 is required. However, if a patient has not had a RHC completed within 36 months of planned Day 1, it should be performed after the patient has signed Informed Consent and has passed the Screening eligibility procedures.

In addition, data resulting from a RHC performed within 36 months 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.

9.10.16. Pregnancy Test

WOCBP (see Section 9.8) will complete a pregnancy test as indicated in Table 3, or at any 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.

9.10.17. Study Drug Administration

Patients should self-administer one capsule from each bottle included in the study drug kit orally once a day, preferably in the morning, as indicated in Table 3. On days when PK samples are

collected, patients must not self-administer study drug. Study staff will administer study drug at the clinic following collection of the first PK sample.

At the Week 24 visit, patients who opt to participate in a sub-study of 24-hr PK must not administer study drug before either day of the Week 24 visit. On the second day of the Week 24 visit, patients must administer study drug after the 24-hr PK blood collection has been performed.

A vomited dose must not be replaced. A double dose (*e.g.*, missed dose from previous day and dose for current day) must not be taken.

9.10.18. Study Drug Dispensation and Collection

Study drug will be dispensed to the patient and collected from the patient as indicated in Table 3. The patient will be dispensed one treatment kit at Day 1 and Week 4; two treatment kits will be dispensed at Week 8 and Week 16. Dispensed treatment kits from each visit should be returned to the site for collection at the subsequent visit.

9.10.19. Telephone Contact

Patients will be contacted by telephone as indicated in Table 3. Patients will be asked about their body weight and other signs of fluid retention, as well as adverse events and any changes to concomitant medications. If fluid retention is suspected, the patient must be brought into the clinic and evaluated by the investigator as soon as possible, as detailed in Section 9.1.1.

9.10.20. Adverse Event Collection

Patients will be observed for general appearance, presence of illness or injury, or signs indicative of a concurrent illness as indicated in Table 3. Patients must be instructed to volunteer any information regarding AEs on or after the first dose of study drug 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. Patients must 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.

9.10.21. Clinical Chemistry

Samples will be collected for the following clinical chemistry analyses as indicated in Table 3: ferritin, creatine kinase (CK), blood urea nitrogen (BUN), creatinine, total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), sodium, potassium, calcium, phosphorus, uric acid, total protein, glucose, albumin, lactate dehydrogenase (LDH), magnesium, chloride, bicarbonate, gamma-glutamyl transpeptidase (GGT). Women of child-bearing potential will require a serum pregnancy test (hCG-Qual) at Screening or at any point in time if a pregnancy is suspected.

9.10.22. N-Terminal Pro-Brain Natriuretic Peptide (NT-Pro BNP) and Brain Natriuretic Peptide (BNP)

Samples will be collected for NT-Pro BNP and BNP as indicated in Table 3. As recent exercise may affect BNP and NT-Pro BNP levels, 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 or at least one hour after 6MWT. This sample must be taken with the patient in the same position at all appropriate visits, *e.g.*, sitting or semi-recumbent.

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

9.10.23. Hematology

Samples will be collected for the following hematology assessments as indicated in Table 3: 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).

9.10.24. Urinalysis and Microscopy

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

9.10.25. Virus Serology

Blood samples will be collected for testing for hepatitis B and hepatitis C as indicated in Table 3. 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.

9.10.26. 6-Minute Walk Test

A 6-minute walk test (6MWT) will be administered to patients as indicated in Table 3. Unless otherwise indicated as described below, each test must be performed in strict accordance with the American Thoracic Society (ATS) guidelines [ATS Statement 2002] provided in Section 19 Appendix 1. The appropriate language version will be applied for patients with a non-English informed consent. The walking course must be 30 m in length, except at sites granted prior sponsor agreement.

Determination of eligibility for 6MWD is based on the 6MWTs performed on separate days at Screening and Day 1. If a Screen B 6MWT is performed, 6MWD eligibility is based on the Screen B and Day 1 6MWDs. Otherwise, 6MWD eligibility is based on the Screen A and Day 1 6MWDs.

The two 6MWD values used to determine eligibility must have a percent difference ≤ 15%, as determined by the following calculation:

$$\text{Percent Difference} = |X-Y| / ((X+Y)/2)$$

X=1st 6MWD value (Screen A or Screen B)

Y=2nd 6MWD value (Day 1)

|X-Y|=absolute value of the difference between the two 6MWD values

[redacted]

The assessor of the 6MWT must not provide the patient with the results of the assessment once complete. A patient should wear the same shoes for all 6MWTs. Additionally, if a patient uses a walking aide for the first test, this same aide should be used during all subsequent tests. The shoes worn and walking aid used for each 6MWT should be noted in source documents.

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.

9.10.27. [redacted]

[redacted]

9.10.28. Quality of Life

[redacted]

9.10.29. WHO/NYHA Functional Class Assessment

WHO/NYHA functional class will be assessed (Section 20, Appendix 2) as indicated in Table 3 [redacted] To the extent feasible, the same evaluator should assess WHO/NYHA FC for a particular patient over the entire course of the study. [redacted]

[redacted]

9.10.32. Pharmacokinetic (PK) Blood Samples

Blood samples for determination of plasma bardoxolone methyl and potential metabolite concentrations will be drawn as indicated in Table 3. Patients must be instructed to not take their study drug prior to coming to the clinic for visits when PK samples will be collected. Patients will be asked by site personnel to provide the time of their last two administrations of study drug prior to the blood samples being collected. 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.

Patients may participate in an optional PK sub-study, which will involve additional PK blood draws prior to dosing and 1, 2, 3, 4, 6, 8, and 24 hours after dose administration during the 2-day Week 24 visit. Patients who participate in the PK sub-study will also have PK blood draws collected during the Week 8 visit as indicated in Table 3. Patients not participating in the PK sub-study may have blood collected on either day of the Week 24 visit.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

Bardoxolone methyl capsules, 2.5 mg and 5 mg, will be used in this study.

10.2. Study Drug Packaging and Labeling

The study drug will be supplied in tamper-evident kits containing two 30-cc high-density polyethylene (HDPE) bottles. Each bottle will utilize foil induction-seal liners and a child-resistant closure. Each bottle of study drug will contain 30 capsules of 2.5 mg or 5 mg strength bardoxolone methyl or the matching placebo capsules. Each bottle will also contain a desiccant insert that must not be ingested. Labeling on each kit bottle will contain at minimum the following information:

- Medication ID number;
- Protocol 402-C-1504;
- Caution Statement: New Drug – Limited by Federal Law to Investigational Use. Keep out of sight and reach of children;
- Control or lot number
- Store at 20° – 25°C (68° – 77°F), short term excursions allowed to 15° – 30°C (59° – 86°F);
- Reata Pharmaceuticals, Inc., Irving, TX.

A double panel label will be presented on the treatment kit carton containing this and other information as well. 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 has been and is currently 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), with brief excursions allowed to 15° – 30°C (59° – 86°F).

10.4. Study Drug Administration

Please refer to Section 9.10.17 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. Patients must be instructed to continue taking study drug once daily up through their Week 24 visits unless: (1) patient has been otherwise instructed by the investigator or (2) the patient has 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 Sponsors' designee. No study drug shall be destroyed by the clinical site unless directed in writing to do so by the Sponsor's quality assurance department. Study drug bottles and any unused capsules should be returned to the study staff for eventual disposition by the Sponsor. The number of capsules returned at each visit will be recorded for each bottle in the kit.

10.6. Study Drug Handling and Disposal

At the conclusion of the study or in an instance of planned study drug replacement, the Sponsor or its designee will direct the site regarding the final disposition of 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, 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 drug. 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 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 that occur during the study (from the time of the first dose of study drug until the final visit indicated in Table 3, 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, as appropriate), regardless of their relationship to study drug or their clinical significance.

The Sponsor, or the Contract Research Organization (CRO) on the behalf of the Sponsor, must be notified immediately regarding the occurrence of any SAE that occurs after the patient is randomized and throughout the study, regardless of study drug administration, including SAEs resulting from protocol-associated procedures, as defined in relevant legislation. The procedures for reporting all SAEs, regardless of causal relationship, are as follows:

- Record the SAE on the AE eCRF and complete the "Serious Adverse Event Report" form within the electronic database.
- In the event the electronic database is not functional, a paper SAE form will be available for the reporting of SAEs.

The Sponsor may request additional information from the investigator to ensure the timely completion of accurate safety reports.

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:

Not Related: This relationship suggests that there is no association between the study drug and the reported event.

Unlikely Related: 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.

Possibly Related: 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.

Probably Related: 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.

Definitely Related: This relationship suggests that a definite causal relationship exists between the drug administration and the AE, and other conditions (*e.g.*, concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

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 28 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 (possibly, probably, or definitely related, 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, 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 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 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.

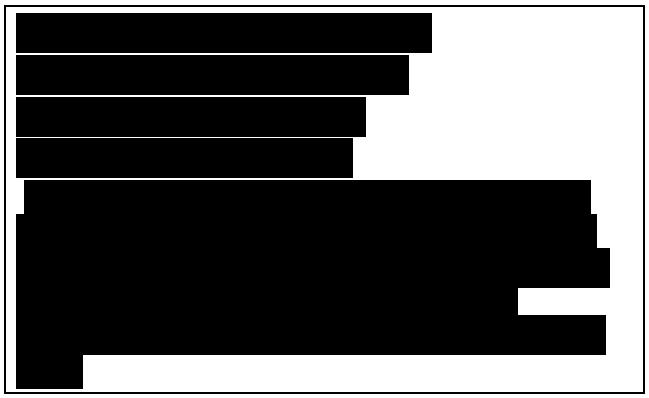
Elective procedures (surgeries or therapies) that were scheduled prior to the start of AE collection are not considered AEs. These elective procedures should not be recorded as AEs, but should be documented in the patient's source documents as elective (*e.g.*, elective periodontal surgery). However, 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. The eCRF system within the clinical database is the preferred method of reporting an SAE.

To report the SAE, the investigator will complete the SAE form in the clinical database and submit [redacted] (Refer to Table 6) within 24 hours of awareness. If the clinical database is down for any reason, the manual SAE forms should be used; however, sites are responsible for ensuring the information on the manual SAE forms is entered into the clinical database once available.

Table 6: SAE Reporting Contact Information



For questions regarding SAE reporting, contact your study manager, monitor,

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 SAE form should be updated within the clinical database and submitted along with any supporting documentation (*e.g.*, subject discharge summary or autopsy reports) (refer to Table 6). If the clinical database is down for any reason, the manual SAE forms should be used; however, sites are responsible for ensuring the updated information on the manual SAE forms is entered into the clinical database once available.

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

[redacted]

- [redacted]
- [redacted]
- [redacted]

12.2. Study Variables

12.2.1. Pharmacokinetic Variables

The pharmacokinetic variables include bardoxolone methyl plasma concentration-time data, and estimated pharmacokinetic parameters for each analyte.

12.2.2. Efficacy Variables

The primary efficacy variable is the change from baseline in 6MWD. The secondary efficacy variable is the time-to-first clinical improvement event. [redacted]

12.2.3. Safety Variables

The safety variables include results of physical examinations, laboratory test results (clinical chemistry, hematology, urinalysis and microscopy), vital sign measurements, ECG results, weight, 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 validated 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, relevant quartiles, standard deviation, coefficient of variation, and geometric mean (where applicable). Categorical data will be summarized using frequency counts and percentages.

12.3.1. Primary Analysis of Efficacy

The intent-to-treat (ITT) population, which includes all randomized patients who received at least one dose of study medication, will be used as the primary population for assessment of efficacy. Likelihood-based estimation with mixed-model repeated measures (MMRM) analysis will compare the treatment groups with respect to the primary endpoint. The dependent variable will be change from baseline in 6MWD. The model will include treatment, visit, and the treatment-by-visit interactions as fixed effects; stratification by number of background PAH therapies (0, 1, or 2); and visit as a repeated measure having an unstructured covariance structure. Covariates may be defined in the SAP as appropriate. Missing data will not be imputed for the primary analysis.

To assess the assumption of missing at random (MAR), a tipping point approach for imputing missing data will be performed as a sensitivity analysis. Shift parameters will adjust the imputed values for observations in the treatment group, not the placebo group, until the p-value > 0.05. Multiple imputation will be used for missing data. Other sensitivity analyses may be performed as appropriate.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

The study monitor, as a representative of the Sponsor, is obligated to follow the study conduct closely. In doing so, the monitor will visit the principal investigator and study facilities periodically, and will maintain 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 inspections, 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), and 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 of the investigator's clinical site, including CTM/IMP storage facilities.

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.

No potential investigator who has a vested financial interest in the success of this study may 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 the 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 authorities, 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 that arise after the approval of the protocol must be documented as protocol amendments. The 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. A 21 CFR Part 11 compliant Electronic Data Capture system (EDC) will be used to capture data electronically for all randomized patients.

17. PUBLICATION POLICY

The Sponsor supports communication and publication of study results whatever the findings of the study.

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 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 any potential publications committee for the study.

18. REFERENCES

ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS Statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-7.

Batt J, Ahmed SS, Correa J, *et al*. Skeletal muscle dysfunction in idiopathic pulmonary arterial hypertension. Am J Respir Cell Mol Biol 2014;50:74-86.

Chung L, Domsic RT, Lingala B, *et al.* Survival and predictors of mortality in systemic sclerosis-associated pulmonary arterial hypertension: outcomes from the pulmonary hypertension assessment and recognition of outcomes in scleroderma registry. Arthritis Care Res 2014;66:489-95.

Dinkova-Kostova AT, Liby KT, Stephenson KK, *et al*. Extremely potent triterpenoid inducers of the phase 2 response: Correlations of protection against oxidant and inflammatory stress. Proc Natl Acad Sci USA 2005;102:4584-9.

Eba S, Hoshikawa Y, Moriguchi T, *et al*. The Nrf2 activator oltipraz attenuates chronic hypoxia-induced cardiopulmonary alterations in mice. Am J Respir Cell Mol Biol 2013;49:324-33.

Galiè N, Hoeper MM, Humbert M, *et al*. ESC Committee for Practice Guidelines (CPG). Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30:2493-537.

Ghofrani HA, Galiè N, Grimminger F, *et al.* Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med 2013;369:330-40.

Holmström KM, Baird L, Zhang Y, *et al.* Nrf2 impacts cellular bioenergetics by controlling substrate availability for mitochondrial respiration. Biol Open 2013;0:1-10.

Lee D-F, Kuo H-P, Liu M, *et al*. KEAP1 E3 ligase-mediated downregulation of NF-kB signaling by targeting IKKß. Molecular Cell 2009;36:131-40.

Li J, Stein TD, Johnson JA. Genetic dissection of systemic autoimmune disease in Nrf2-deficient mice. Physiol Genomics 2004;18:261-72.

Ludtmann MH, Angelova PR, Zhang Y, *et al.* Nrf2 impacts the efficiency of mitochondrial fatty acid oxidation. Biochem J 2014;457:415-24.

Mainguy V, Maltais F, Saey D, *et al*. Peripheral muscle dysfunction in idiopathic pulmonary hypertension. Thorax 2010;65:113-7.

Malenfant S, Potus F, Fournier F, *et al*. Skeletal muscle proteomic signature and metabolic impairment in pulmonary hypertension. J Mol Med 2015;93:573-84.

Osburn WO & Kensler TW. Nrf2 signaling: An adaptive response pathway for protection against environmental toxic insults. Mutat Res 2008;669:31-9.

Price L, Caramori G, Dorfmuller P, *et al*. Endothelial cell NF-kB activation is increased in human idiopathic PAH. Thorax 2010;65:A88-A89.

Pugh, ME; Robbins, IM; Rice, TW, *et al*. Unrecognized glucose intolerance is common in pulmonary arterial hypertension. J Heart Lung Transplant 2011;30:904-11.

Rojas-Rivera J, Ortiz A, Egido J. Antioxidants in kidney diseases: The impact of bardoxolone methyl. Int J Nephrol 2012;2012:1-11.

Saha P, Reddy V, Konopleva M, *et al*. The triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic-acid methyl ester has potent antidiabetic effects in diet-induced diabetic mice and Lepr(db/db) mice. J Biol Chem 2010;285:40581-92.

Sutendra G, Michelakis ED. The metabolic basis of pulmonary arterial hypertension. Cell Metab 2014;19:558-73.

Tapson VF, Jing ZC, Xu KF, *et al*. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients receiving background endothelin receptor antagonist and phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C2 study): a randomized controlled trial. Chest 2013;144:952-8.

Wei J, Zhu H, Komura K, *et al.* A synthetic PPAR-γ agonist triterpenoid ameliorates experimental fibrosis: PPAR-γ-independent suppression of fibrotic responses. Ann Rheum Dis 2014;73:446-54.

Wu QQ, Wang Y, Senitko M, *et al*. Bardoxolone methyl (BARD) ameliorates ischemic AKI and increases expression of protective genes Nrf2, PPARgamma, and HO-1. Am J Physiol Renal Physiol 2011;300:F1180-F1192.

Wu T, Ye Y, Min SY, *et al.* Prevention of murine lupus nephritis by targeting multiple signaling axes and oxidative stress using a synthetic triterpenoid. Arthritis Rheumatol 2014;66:3129-39.

Yoh K, Itoh K, Enomoto A, *et al.* Nrf2-deficient female mice develop lupus-like autoimmune nephritis. Kidney Int 2001;60:1343-53.

19. APPENDIX 1: ATS GUIDELINES FOR THE SIX-MINUTE WALK TEST

American Thoracic Society

ATS Statement: Guidelines for the Six-Minute Walk Test

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS APPROVED BY THE ATS BOARD OF DIRECTORS MARCH 2002

CONTENTS

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. These recommendations are not intended to limit the use of alternative protocols for research studies. We do not discuss the general topic of clinical exercise testing.

As with other American Thoracic Society statements on pulmonary function testing, these guidelines come out of a consensus conference. Drafts were prepared by two members (P.L.E. and R.J.Z.) and were based on a comprehensive Medline literature search from 1970 through 2001, augmented by suggestions from other committee members. Each draft responded to comments from the working committee. The guidelines follow previously published methods as closely as possible and provide a rationale for each specific recommendation. The final recommendations represent a consensus of the committee. The committee recommends that these guidelines be reviewed in five years and in the meantime encourages further research in areas of controversy.

BACKGROUND

There are several modalities available for the objective evaluation of functional exercise capacity. Some provide a very complete assessment of all systems involved in exercise performance (high tech), whereas others provide basic information but are low tech and are simpler to perform. The modality used should be chosen based on the clinical question to be addressed and on available resources. The most popular clinical exercise tests in order of increasing complexity are stair climbing, a 6MWT, a shuttle-walk test, detection of exercise-induced asthma, a cardiac stress test (e.g., Bruce protocol), and a cardiopulmonary exercise test (1, 2). Other professional organizations have published standards for cardiac stress testing (3, 4).

Assessment of functional capacity has traditionally been done by merely asking patients the following: "How many flights of stairs can you climb or how many blocks can you walk?" However, patients vary in their recollection and may report overestimations or underestimations of their true functional capacity. Objective measurements are usually better than self-reports. In the early 1960s, Balke developed a simple test to evaluate the functional capacity by measuring the distance walked during a defined period of time (5). A 12-minute field performance test was then developed to evaluate the level of physical fitness of healthy individuals (6). The walking test was also adapted to assess disability in patients with chronic bronchitis (7). In an attempt to accommodate patients with respiratory disease for whom walking 12 minutes was too exhausting, a 6-minute walk was found to perform as well as the 12-minute walk (8). A recent review of functional walking tests concluded that "the 6MWT is easy to administer, better tolerated, and more reflective of activities of daily living than the other walk tests" (9).

The 6MWT is a practical simple test that requires a 100-ft 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 quickly walk on a flat, hard surface in a period of 6 minutes (the 6MWD). 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 6MWD may better reflect the functional exercise level for daily physical activities.

INDICATIONS AND LIMITATIONS

The strongest indication for the 6MWT is for measuring the response to medical interventions in patients with moderate to severe heart or lung disease. The 6MWT has also been used as a one-time measure of functional status of patients, as well as a predictor of morbidity and mortality (*see* Table 1 for a list of these indications). The fact that investigators have used the 6MWT in these settings does not prove that the test is clinically useful (or the best test) for determining functional capacity or changes in functional capacity due to an intervention in patients with these diseases. Further studies are necessary to determine the utility of the 6MWT in various clinical situations.

Am J Respir Crit Care Med Vol 166. pp 111–117, 2002
DOI: 10.1164/rccm.166/1/111
Internet address: www.atsjournals.org

Formal cardiopulmonary exercise testing provides a global assessment of the exercise response, an objective determination of functional capacity and impairment, determination of the appropriate intensity needed to perform prolonged exercise, quantification of factors limiting exercise, and a definition of the underlying pathophysiologic mechanisms such as the contribution of different organ systems involved in exercise. The 6MWT does not determine peak oxygen uptake, diagnose the cause of dyspnea on exertion, or evaluate the causes or mechanisms of exercise limitation (1, 2). The information provided by a 6MWT should be considered complementary to cardiopulmonary exercise testing, not a replacement for it. Despite the difference between these two functional tests, some good correlations between them have been reported. For example, a significant correlation ($r = 0.73$) between 6MWD and peak oxygen uptake has been reported for patients with end-stage lung diseases (36, 37).

In some clinical situations, the 6MWT provides information that may be a better index of the patient's ability to perform daily activities than is peak oxygen uptake; for example, 6MWD correlates better with formal measures of quality of life (38). Changes in 6MWD after therapeutic interventions correlate with subjective improvement in dyspnea (39, 40). The reproducibility of the 6MWD (with a coefficient of variation of approximately 8%) appears to be better than the reproducibility of 1-second forced expiratory volume in patients with chronic obstructive pulmonary disease (COPD) (8, 41–43). Questionnaire indices of functional status have a larger short-term variability (22–33%) than does the 6MWD (37).

The shuttle-walking test is similar to the 6MWT, but it uses an audio signal from a tape cassette to direct the walking pace of the patient back and forth on a 10-m course (44–47). The walking speed is increased every minute, and the test ends when the patient cannot reach the turnaround point within the required time. The exercise performed is similar to a symptom-limited, maximal, incremental treadmill test. An advantage of the shuttle walking test is that it has a better correlation with peak oxygen uptake than the 6MWD. Disadvantages include less validation, less widespread use, and more potential for cardiovascular problems.

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 heart rate of more than 120, a systolic blood pressure of more than 180 mm Hg, and a diastolic blood pressure of more than 100 mm Hg.

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 (31, 48–50) and thousands of patients with heart failure or cardiomyopathy (32, 51, 52) 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.

TABLE 1. INDICATIONS FOR THE SIX-MINUTE WALK TEST

Pretreatment and posttreatment comparisons
Lung transplantation (9, 10)
Lung resection (11)
Lung volume reduction surgery (12, 13)
Pulmonary rehabilitation (14, 15)
COPD (16–18)
Pulmonary hypertension
Heart failure (19, 20)
Functional status (single measurement)
COPD (21, 22)
Cystic fibrosis (23, 24)
Heart failure (25–27)
Peripheral vascular disease (28, 29)
Fibromyalgia (30)
Older patients (31)
Predictor of morbidity and mortality
Heart failure (32, 33)
COPD (34, 35)
Primary pulmonary hypertension (10, 36)

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

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). A telephone or other means should be in place to enable a call for help.
3. 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.
4. 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.
5. 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: blood pressure, 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. If the weather is comfortable, the test may be performed outdoors. The walking course must be 30 m in length. A 100-ft hallway is, therefore, required. The length of the corridor should be marked every 3 m. 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 60-m 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 6MWD. Most studies have used a 30-m corridor, but some have used 20- or 50-m corridors (52–55). A recent multicenter study found no significant effect of the length of straight courses ranging from 50 to 164 ft, but patients walked farther on continuous (oval) tracks (mean 92 ft farther) (54).

The use of a treadmill to determine the 6MWD might save space and allow constant monitoring during the exercise, but the use of a treadmill for 6-minute walk testing is not recommended. Patients are unable to pace themselves on a treadmill. In one study of patients with severe lung disease, the mean distance walked on the treadmill during 6 minutes (with the speed adjusted by the patients) was shorter by a mean of 14% when compared with the standard 6MWD using a 100-ft hallway (57). The range of differences was wide, with patients walking between 400–1,300 ft on the treadmill who walked 1,200 ft in the hallway. Treadmill test results, therefore, are not interchangeable with corridor tests.

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.
3. Patients should use their usual walking aids during the test (cane, walker, etc.).
4. The patient's usual medical regimen should be continued.
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, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Compete the first portion of the worksheet (*see* the APPENDIX).
4. Pulse oximetry is optional. If it is performed, measure and record baseline heart rate and oxygen saturation (SpO_2) and follow manufacturer's instructions to maximize the signal and to minimize motion artifact (56, 57). 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 (39). 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. (57)

5. Have the patient stand and rate their baseline dyspnea and overall fatigue using the Borg scale (*see* Table 2 for the Borg scale and instructions [58]).
6. 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.
7. 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."

TABLE 2. THE BORG SCALE

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very severe
8	
9	
10	Very, very severe (maximal)

This Borg scale should be printed on heavy paper (11 inches high and perhaps laminated) in 20-point type size. At the beginning of the 6-minute exercise, show the scale to the patient and ask the patient this: "Please grade your level of shortness of breath using this scale." Then ask this: "Please grade your level of fatigue using this scale."

At the end of the exercise, remind the patient of the breathing number that they chose before the exercise and ask the patient to grade their breathing level again. Then ask the patient to grade their level of fatigue, after reminding them of their grade before the exercise.

8. 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.
9. 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.

   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: "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.
10. Post-test: Record the postwalk Borg dyspnea and fatigue levels and ask this: "What, if anything, kept you from walking farther?"
11. If using a pulse oximeter, measure SpO_2 and pulse rate from the oximeter and then remove the sensor.
12. Record the number of laps from the counter (or tick marks on the worksheet).
13. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.
14. Congratulate the patient on good effort and offer a drink of water.

QUALITY ASSURANCE

Sources of Variability

There are many sources of 6MWD variability (*see* Table 3). 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.

Practice Tests

A practice test is not needed in most clinical settings but should be considered. If a practice test is done, wait for at least 1 hour before the second test and report the highest 6MWD as the patient's 6MWD baseline.

Rationale. The 6MWD is only slightly higher for a second 6MWT performed a day later. The mean reported increase ranges from 0 to 17% (23, 27, 40, 41, 54, 59). A multicenter study of 470 highly motivated patients with severe COPD performed two 6MWTs 1 day apart, and on average, the 6MWD was only 66 ft (5.8%) higher on the second day (54).

Performance (without an intervention) usually reaches a plateau after two tests done within a week (8, 60). The training effect may be due to improved coordination, finding optimal stride length, and overcoming anxiety. The possibility of a practice or training effect from tests repeated after more than a month has not been studied or reported; however, it is likely that the effect of training wears off (does not persist) after a few weeks.

Technician Training and Experience

Technicians who perform 6MWTs 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.

Rationale. One multicenter study of older people found that after correction for many other factors, two of the technicians had mean 6MWDs that were approximately 7% lower than the other two sites (31).

Encouragement

Only the standardized phrases for encouragement (as specified previously here) must be used during the test.

Rationale. Encouragement significantly increases the distance walked (42). Reproducibility for tests with and without encouragement is similar. Some studies have used encouragement every 30 seconds, every minute, or every 2 minutes. We have chosen every minute and standard phrases. Some studies (53) have instructed patients to walk as fast as possible. Although larger mean 6MWDs may be obtained thereby, we recommend that such phrases not be used, as they emphasize initial speed at the expense of earlier fatigue and possible excessive cardiac stress in some patients with heart disease.

TABLE 3. 6MWD SOURCES OF VARIABILITY

Factors reducing the 6MWD
Shorter height
Older age
Higher body weight
Female sex
Impaired cognition
A shorter corridor (more turns)
Pulmonary disease (COPD, asthma, cystic fibrosis, interstitial lung disease)
Cardiovascular disease (angina, MI, CHF, stroke, TIA, PVD, AAI)
Musculoskeletal disorders (arthritis, ankle, knee, or hip injuries, muscle wasting, etc.)
Factors increasing the 6MWD
Taller height (longer legs)
Male sex
High motivation
A patient who has previously performed the test
Medication for a disabling disease taken just before the test
Oxygen supplementation in patients with exercise-induced hypoxemia

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; 6MWD = 6-minute walking distance.

Supplemental Oxygen

If oxygen supplementation is needed during the walks and serial tests are planned (after an intervention other than oxygen therapy), then during all walks by that patient oxygen should be delivered in the same way with the same flow. If the flow must be increased during subsequent visits due to worsening gas exchange, this should be noted on the worksheet and considered during interpretation of the change noted in 6MWD. 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). Measurements of pulse and SpO_2 should be made after waiting at least 10 minutes after any change in oxygen delivery.

Rationale. For patients with COPD or interstitial lung disease, oxygen supplementation increases the 6MWD (17, 59, 61, 63). Carrying a portable gas container (but not using it for supplemental oxygen) reduced the mean 6MWD by 14% in one study of patients with severe respiratory disability, but using the container to deliver supplemental oxygen during the exercise increased the mean 6MWD by 20–35% (59).

Medications

The type of medication, dose, and number of hours taken before the test should be noted.

Rationale. Significant improvement in the distance walked, or the dyspnea scale, after administration of bronchodilators has been demonstrated in patients with COPD (62, 63), as well as cardiovascular medications in patients with heart failure (19).

INTERPRETATION

Most 6MWTs will be done before and after intervention, and the primary question to be answered after both tests have been completed is whether the patient has experienced a clinically significant improvement. With a good quality-assurance program, with patients tested by the same technician, and after one or two practice tests, short-term reproducibility of the 6MWD is excellent (37). It is not known whether it is best for clinical purposes to express change in 6MWD as (*1*) an absolute value, (*2*) a percentage change, or (*3*) a change in the percentage of predicted value. Until further research is available, we recommend that change in 6MWD be expressed as an absolute value (e.g., the patient walked 50 m farther).

A statistically significant mean increase in 6MWD in a group of study participants is often much less than a clinically significant increase in an individual patient. In one study of 112 patients (half of them women) with stable, severe COPD, the smallest difference in 6MWD that was associated with a noticeable clinical difference in the patients' perception of exercise performance was a mean of 54 m (95% confidence interval, 37–71 m) (64). This study suggests that for individual patients with COPD, an improvement of more than 70 m in the 6MWD after an intervention is necessary to be 95% confident that the improvement was significant. In an observational study of 45 older patients with heart failure, the smallest difference in 6MWD that was associated with a noticeable difference in their global rating of worsening was a mean of 43 m (20). The 6MWD was more responsive to deterioration than to improvement in heart failure symptoms.

Reported Mean Changes in 6MWD After Interventions

Supplemental oxygen (4 L/min) during exercise in patients with COPD or interstitial lung disease increased mean 6MWD by approximately 95 m (36%) in one study (59). Patients taking an inhaled corticosteroid experienced a mean 33 m (8%) increase in 6MWD in an international COPD study (16). Patients with COPD in a study of the effects of exercise and diaphragmatic strength training experienced a mean increase in 6MWD of 50 m (20%) (65). Lung volume reduction surgery in patients with very severe COPD has been reported to increase 6MWD by a mean of 55 m (20%) (13).

Cardiac rehabilitation in patients referred with various heart diseases increased 6MWD by a mean of 170 m (15%) in a recent study (66). In 25 older patients with heart failure, an angiotensin-converting enzyme inhibitor medication (50 mg captopril per day) improved 6MWD a mean of 64 m (39%) compared with a mean increase of only 8% in those receiving a placebo (19).

Interpreting Single Measurements of Functional Status

Optimal reference equations from healthy population-based samples using standardized 6MWT methods are not yet available. In one study, the median 6MWD was approximately 580 m for 117 healthy men and 500 m for 173 healthy women (50). A mean 6MWD of 630 m was reported by another study of 51 healthy older adults (55). Differences in the population sampled, type and frequency of encouragement, corridor length, and number of practice tests may account for reported differences in mean 6MWD in healthy persons. Age, height, weight, and sex independently affect the 6MWD in healthy adults; therefore, these factors should be taken into consideration when interpreting the results of single measurements made to determine functional status. We encourage investigators to publish reference equations for healthy persons using the previously mentioned standardized procedures.

A low 6MWD is nonspecific and nondiagnostic. When the 6MWD is reduced, a thorough search for the cause of the impairment is warranted. The following tests may then be helpful: pulmonary function, cardiac function, ankle–arm index, muscle strength, nutritional status, orthopedic function, and cognitive function.

Conclusions

The 6MWT is a useful measure of functional capacity targeted at people with at least moderately severe impairment. The test has been widely used for preoperative and postoperative evaluation and for measuring the response to therapeutic interventions for pulmonary and cardiac disease. These guidelines provide a standardized approach to performing the 6MWT. The committee hopes that these guidelines will encourage further research into the 6MWT and allow direct comparisons among different studies.

This statement was developed by the ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories.

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References

1. Wasserman K, Hansen JE, Sue DY, Casaburi R, Whipp BJ. Principles of exercise testing and interpretation, 3rd edition. Philadelphia: Lippincott, Williams & Wilkins; 1999.

2. Weisman IM, Zeballos RJ. An integrated approach to the interpretation of cardiopulmonary exercise testing. *Clin Chest Med* 1994;15:421–445.
3. Fletcher GF, Balady G, Froelicher VF, Hartley LH, Haskell WL, Pollock ML. Exercise standards: a statement for healthcare professionals from the American Heart Association: writing group. *Circulation* 1995; 91:580–615.
4. Pina IL, Balady GJ, Hanson P, Labovitz AJ, Madonna DW, Myers J. Guidelines for clinical exercise testing laboratories: a statement for healthcare professionals from the Committee on Exercise and Cardiac Rehabilitation, American Heart Association. *Circulation* 1995;91:912–921.
5. Balke B. A simple field test for the assessment of physical fitness. *CARI Report* 1963;63:18.
6. Cooper KH. A means of assessing maximal oxygen intake: correlation between field and treadmill testing. *JAMA* 1968;203:201–204.
7. McGavin CR, Gupta SP, McHardy GJR. Twelve-minute walking test for assessing disability in chronic bronchitis. *BMJ* 1976;1:822–823.
8. Butland RJA, Pang J, Gross ER, Woodcock AA, Geddes DM. Two-, six-, and 12-minute walking tests in respiratory disease. *BMJ* 1982; 284:1607–1608.
9. Solway S, Brooks D, Lacasse Y, Thomas S. A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. *Chest* 2001;119:256–270.
10. Kadikar A, Maurer J, Kesten S. The six-minute walk test: a guide to assessment for lung transplantation. *J Heart Lung Transplant* 1997;16: 313–319.
11. Holden DA, Rice TW, Stelmach K, Meeker DP. Exercise testing, 6 min walk, and stair climb in the evaluation of patients at high risk for pulmonary resection. *Chest* 1992;102:1774–1779.
12. Sciurba FC, Rogers RM, Keenan RJ, Slivka WA, Gorcsan J 3rd, Ferson PF, Holbert JM, Brown ML, Landreneau RJ. Improvement in pulmonary function and elastic recoil after lung-reduction surgery for diffuse emphysema. *N Engl J Med* 1996;334:1095–1099.
13. Criner GJ, Cordova FC, Furukawa S, Kuzma AM, Travaline JM, Leyenson V, O'Brien GM. Prospective randomized trial comparing bilateral lung volume reduction surgery to pulmonary rehabilitation in severe COPD. *Am J Respir Crit Care Med* 1999;160:2018–2027.
14. Sinclair DJM, Ingram CG. Controlled trial of supervised exercise training in chronic bronchitis. *BMJ* 1980;280:519–521.
15. Roomi J, Johnson MM, Waters K, Yohannes A, Helm A, Connolly MJ. Respiratory rehabilitation, exercise capacity and quality of life in chronic airways disease in old age. *Age Ageing* 1996;25:12–16.
16. Paggiaro PL, Dahle R, Bakran I, Frith L, Hollingworth K, Efthimiou J. Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with COPD. *Lancet* 1998;351:773–780.
17. Leggett RJ, Flenley DC. Portable oxygen and exercise tolerance in patients with chronic hypoxic cor pulmonale. *BMJ* 1977;2:84–86.
18. Spence DPS, Hay JG, Carter J, Pearson MG, Calverley PMA. Oxygen desaturation and breathlessness during corridor walking in COPD: effect of oxitropium bromide. *Thorax* 1993;48:1145–1150.
19. DeBock V, Mets T, Romagnoli M, Derde MP. Captopril treatment of chronic heart failure in the very old. *J Gerontol* 1994;49:M148–M152.
20. O'Keeffe ST, Lye M, Donnnellan C, Carmichael DN. Reproducibility and responsiveness of quality of life assessment and six minute walk test in elderly heart failure patients. *Heart* 1998;80:377–382.
21. Bernstein ML, Despars JA, Singh NP, Avalos K, Stansbury DW, Light RW. Re-analysis of the 12 minute walk in patients with COPD. *Chest* 1994;105:163–167.
22. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Koyama H, Izumi T. Analysis of clinical methods used to evaluate dyspnea in patients with COPD. *Am J Respir Crit Care Med* 1998;158:1185–1189.
23. Gulmans VAM, vanVeldhoven NHMJ, deMeer K, Helders PJM. The six-minute walking test in children with cystic fibrosis: reliability and validity. *Pediatr Pulmonol* 1996;22:85–89.
24. Nixon PA, Joswiak ML, Fricker FJ. A six-minute walk test for assessing exercise tolerance in severely ill children. *J Pediatr* 1996;129:362–366.
25. Bittner V. Six-minute walk test in patients with cardiac dysfunction. *Cardiologia* 1997;42:897–902.
26. Peeters P, Mets T. The 6 minute walk as an appropriate exercise test in elderly patients with chronic heart failure. *J Gerontol* 1996;51A: M147–M151.
27. Zugck C, Kruger C, Durr S, Gerber SH, Haunstetter A, Hornig K, Kubler W, Haass M. Is the 6-minute walk test a reliable substitute for peak oxygen uptake in patients with dilated cardiomyopathy? *Eur Heart J* 2000;21:540–549.
28. Montogomery PS, Gardner AW. The clinical utility of a six-minute walk test in peripheral arterial occlusive disease patients. *J Am Geriatr Soc* 1998;46:706–711.
29. Cahan MA, Montgomery P, Otis RB, Clancy R, Flinn W, Gardner A. The effect of cigarette smoking status on six-minute walk distance in patients with intermittent claudication. *Angiology* 1999;50:537–546.
30. King S, Wessel J, Bhambhani Y, Maikala R, Sholter D, Maksymowych W. Validity and reliability of the 6 minute walk in persons with fibromyalgia. *J Rheumatol* 1999;26:2233–2237.
31. Enright PL, McBurnie MA, Bittner V, Tracy RP, McNamara R, Newman AB, the Cardiovascular Health Study. The six minute walk test: a quick measure of functional status in elderly adults. *Chest* (In press)
32. Bittner V, Weiner DH, Yusuf S, Rogers WJ, McIntyre KM, Bangdiwala SI, Kronenberg MW, Kostis JB, Kohn RM, Guillotte M, *et al*. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. *JAMA* 1993;270:1702–1707.
33. Cahalin LP, Mathier MA, Semigran MJ, Dec GW, DiSalvo TG. The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. *Chest* 1996;110:325–332.
34. Cote CG, Celli BR. In patients with COPD, the 6 minute walking distance is a better predictor of health care utilization than FEV1, blood gases, and dyspnea [abstract]. *Eur Respir J* 1998;383.
35. Kessler R, Faller M, Fourgaut G, Mennecier B, Weitzenblum E. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;159:158–164.
36. Cahalin L, Pappagianopoulos P, Prevost S, Wain J, Ginns L. The relationship of the 6-min walk test to maximal oxygen consumption in transplant candidates with end-stage lung disease. *Chest* 1995;108:452–459.
37. Guyatt GH, Thompson PJ, Berman LB, Sullivan MJ, Townsend M, Jones NL, Pugsley SO. How should we measure function in patients with chronic heart and lung disease? *J Chronic Dis* 1985;38:517–524.
38. Guyatt GH, Townsend M, Keller J, Singer J, Nogradi S. Measuring functional status in chronic lung disease: conclusions from a random control trial. *Respir Med* 1991;85(Suppl B):17–21.
39. Niederman MS, Clemente PH, Fein AM, Feinsilver SH, Robinson DA, Ilowite JS, Bernstein MG. Benefits of a multidisciplinary pulmonary rehabilitation program: improvements are independent of lung function. *Chest* 1991;99:798–804.
40. Noseda A, Carpiaux J, Prigogine T, Schmerber J. Lung function, maximum and submaximum exercise testing in COPD patients: reproducibility over a long interval. *Lung* 1989;167:247–257.
41. Knox AJ, Morrison JF, Muers MF. Reproducibility of walking test results in chronic obstructive airways disease. *Thorax* 1988;43:388–392.
42. Guyatt GH, Pugsley SO, Sullivan MJ, Thompson PJ, Berman LB, Jones NL, Fallen EL, Taylor DW. Effect of encouragement on walking test performance. *Thorax* 1984;39:818–822.
43. Leger LA. A maximal multistage 20-m shuttle run test to predict VO2 max. *Eur J Appl Physiol* 1982;49:1–12.
44. Singh SJ, Morgan MDL, Scott S, Walters D, Hardman AE. Development of a shuttle walking test of disability in patients with chronic airways obstruction. *Thorax* 1992;47:1019–1024.
45. Revill SM, Morgan MDL, Singh SJ, Williams J, Hardman AE. The endurance shuttle walk: a new field test for the assessment of endurance capacity in chronic obstructive pulmonary disease. *Thorax* 1999;54:213–222.
46. Singh SJ, Morgan MDL, Hardman AE, Rowe C, Bardsley PA. Comparison of oxygen uptake during a conventional treadmill test and the shuttle walking test in chronic airflow limitation. *Eur Respir J* 1994;7: 2016–2020.
47. Morales FJ, Martinez A, Mendez M, Agarrado A, Ortega F, Fernandez-Guerra J, Montemayor T, Burgos J. A shuttle walk test for assessment of functional capacity in chronic heart failure. *Am Heart J* 1999;138:292–298.
48. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med* 1998;158:1384–1387.
49. Barst RJ, Rubin LJ, McGoon MD, Caldwell EJ. Long WA, Levy PS. Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. *Ann Intern Med* 1994;121:409–415.
50. Miyamoto S, Nagaya N, Satoh T, Kyotani S, Sakamaki F, Fujita M, Nakanishi N, Miyatake K. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. *Am J Respir Crit Care Med* 2000;161:487–492.
51. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, Berman LB. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J* 1985; 132:919–923.
52. Lipkin DP, Scrivin AJ, Crake T, Poole-Wilson PA. Six minute walking test for assessing exercise capacity in chronic heart failure. *BMJ* 1986; 292:653–655.
53. Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *Eur Respir J* 1999;14:270–274.

54. Weiss RA, *et al.* Six minute walk test in severe COPD: reliability and effect of walking course layout and length. Paper presented at ACCP Conference; September 2000; San Francisco.
55. Stevens D, Elpern E, Sharma K, Szidon P, Ankin M, Kesten S. Comparison of hallway and treadmill six-minute walk tests. *Am J Respir Crit Care Med* 1999;160:1540–1543.
56. Jensen LA, Onyskiw JE, Prasad NGN. Meta-analysis of arterial oxygen saturation monitoring by pulse oximetry in adults. *Heart Lung* 1998; 27:387–408.
57. Barthelemy JC, Geyssant A, Riffat J, Antoniadis A, Berruyer J, LaCour JR. Accuracy of pulse oximetry during moderate exercise: a comparative study. *Scand J Clin Lab Invest* 1990;50:533–539.
58. Borg GAV. Psycho-physical bases of perceived exertion. *Med Sci Sports Exerc* 1982;14:377–381.
59. Leach RM, Davidson AC, Chinn S, Twort CHC, Cameron IR, Batemen NT. Portable liquid oxygen and exercise ability in severe respiratory disability. *Thorax* 1992;47:781–789.
60. Mungall IPF, Hainsworth R. Assessment of respiratory function in patients with chronic obstructive airways disease. *Thorax* 1979;34:254–258.
61. Roberts CM, Bell J, Wedzicha JA. Comparison of the efficacy of a demand oxygen delivery system with continuous low flow oxygen in subjects with stable COPD and severe oxygen desaturation on walking. *Thorax* 1996;51:831–834.
62. Hay JG, Stone P, Carter J, Church S, Eyre-Brook A, Pearson MG, Woodcock AA, Calverley PM. Bronchodilator reversibility, exercise performance and breathlessness in stable chronic obstructive pulmonary disease. *Eur Respir J* 1992;5:659–664.
63. Grove A, Lipworth BJ, Reid P, Smith RP, Lamage L, Ingram CG, Jenkins RJ, Winter JH, Dhillon DP. Effects of regular salmeterol on lung function and exercise capacity in patients with COPD. *Thorax* 1996;51:689–693.
64. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: The six minute walk test in chronic lung disease patients. *Am J Respir Crit Care Med* 1997;155:1278–1282.
65. Weiner P, Magadle R, Berar-Yanay N, Davidovich A, Weiner M. The cumulative effect of long-acting bronchodilators, exercise, and inspiratory muscle training on the perception of dyspnea in patients with advanced COPD. *Chest* 2000;118:672–678.
66. Bittner V, Sanderson B, Breland J, Adams C, Schuman C. Assessing functional capacity as an outcome in cardiac rehabilitation: role of the 6 minute walk test. *Clinical Exercise Physiology* 2000.

APPENDIX

The following elements should be present on the 6MWT worksheet and report:

Lap counter: __

Patient name: _____ Patient ID# _____

Walk # _____ Tech ID: _____ Date: _____

Gender: M F Age: ____ Race: ____ Height: ___ft ____in, ____ meters

Weight: _____ lbs, _____kg Blood pressure: _____ / _____

Medications taken before the test (dose and time): _____

Supplemental oxygen during the test: No Yes, flow _____ L/min, type _____

	Baseline	End of Test
Time	___:___	___:___
Heart Rate	_____	_____
Dyspnea	____	____ (Borg scale)
Fatigue	____	____ (Borg scale)
SpO_2	____ %	____%

Stopped or paused before 6 minutes? No Yes, reason: _____

Other symptoms at end of exercise: angina dizziness hip, leg, or calf pain

Number of laps: ____ (×60 meters) + final partial lap: _____ meters =

Total distance walked in 6 minutes: _____ meters

Predicted distance: _____ meters Percent predicted: _____%

Tech comments:

Interpretation (including comparison with a preintervention 6MWD):

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.

21. [redacted]