BARDOXOLONE METHYL (RTA 402)

402-C-1602

[redacted]

EUDRACT NUMBER: 2016-004365-16

AN EXTENDED ACCESS PROGRAM TO ASSESS LONG-TERM SAFETY OF BARDOXOLONE METHYL IN PATIENTS WITH PULMONARY HYPERTENSION

VERSION 3.2 – 11 JULY 2019

GERMANY

Protocol History

Version 1.0 – 27 October 2016

Version 2.0 – 05 January 2017

Version 2.2 – 23 June 2017

Version 3.1 – 16 July 2018

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-1602 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] Non-North American sites will use access codes specific to their country. Numbers for non-North American sites for SAE reporting will be provided by the clinical team directly to the sites for reporting and submitting SAE information to [redacted].	

2. SYNOPSIS

Name of Sponsor/Company:
Reata Pharmaceuticals, Inc.

Name of Investigational Product:
Bardoxolone methyl

Title of Study:
An Extended Access Program to Assess Long-Term Safety of Bardoxolone Methyl in Patients with Pulmonary Hypertension

Study center(s): Approximately 150 study centers

Studied period: 60 months Estimated date first patient enrolled in Germany: July 2017 Estimated date last patient completed in Germany: July 2023 The study duration may be extended beyond 60 months in a future protocol amendment subject to all applicable regulatory and ethics approvals. The end of the study is defined as the last visit of the last patient.	**Phase of development:** 3a

Primary Objectives:
To provide continuing open-label treatment with bardoxolone methyl as part of this extended access program while collecting ongoing safety and tolerability data of bardoxolone methyl.

Primary Safety Endpoint:
Frequency, intensity, and relationship to study drug of adverse events (AEs) and serious adverse events (SAEs), and change from baseline in the following assessments: physical examinations, vital sign measurements, B-type natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-proBNP), and weight.

Methodology:
This extended access study will assess the long-term safety and tolerability of bardoxolone methyl in qualified patients with pulmonary hypertension (PH) who previously participated in controlled clinical studies with bardoxolone methyl.

Qualified patients will start dosing at 10 mg of bardoxolone methyl every other day, then begin once daily dosing at Week 4 (unless contraindicated clinically) and continue the drug for up to 5 years or until patient withdrawal, whichever is sooner. The treatment duration may be extended in a future protocol amendment subject to all applicable regulatory and ethics approvals. Dose de-escalation (down to 5 mg) is permitted during the study, if indicated clinically.

All patients in the study will follow the same visit and assessment schedule. Patients will be scheduled to be assessed in person during treatment at Day 1, Week 2, Week 4, Week 6, Week 8, Week 24, and every 24 weeks thereafter. Patients will also be assessed by telephone contact on Days 3, 10, 21, 31, and 38. Day 1 for this extended access study should occur on the same day as the last visit in the controlled clinical study. Patient status should be carefully monitored by the investigator during the first 8 weeks of study treatment. Assessments required for both the last visit in the controlled study and Day 1 for this study should only be completed once.

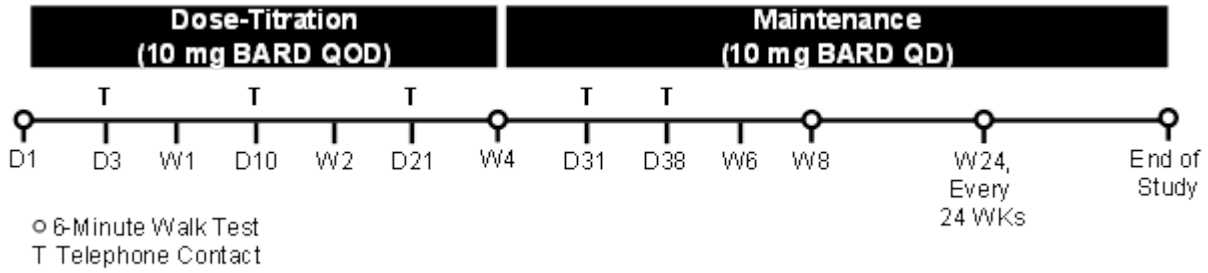
Patients from the CATALYST study:

Day 1 of this extended access study will coincide with the Week 28 follow-up visit for patients from CATALYST (402-C-1504, NCT02657356, EudraCT 2016-000196-24). If this extended access program is not yet open for enrollment at the time of a patient's Week 28 visit, the Day 1 visit (*i.e.*, enrollment) must occur within 30 days of site activation. Exceptions allowing CATALYST patients who have completed 24 weeks of treatment to schedule their follow-up assessments prior to Week 28 and still be considered eligible for this open-label study should be discussed with the Chief Medical Officer at Reata, or designee, and will be considered on a case-by-case basis.

Patients from the LARIAT study:

Day 1 of this extended access study will coincide with the End-of-Study visit for patients from LARIAT (402-C-1302, NCT02036970).

Schema for Study of Bardoxolone Methyl in Patients with Pulmonary Hypertension



Number of patients (planned):

Patient numbers will be determined by those who are treatment-compliant and who have previously participated in clinical studies with bardoxolone methyl.

Main criteria for inclusion:

1. Treatment-compliant patients who are participating in qualifying ongoing studies (CATALYST, EudraCT 2016-000196-24; LARIAT, EudraCT 2016-004793-17) and who have completed required End-of-Treatment and/or Follow-up visits in one of these prior clinical studies with bardoxolone methyl and who, according to the assessment of the investigator, have a potential positive benefit-risk assessment for participating in the trial.
2. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study prior to initiation of any protocol-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;
2. Patients who have an ongoing SAE from a clinical study that is assessed by the investigator as related to bardoxolone methyl;
3. Unwilling to practice acceptable methods of birth control (both males who have partners of childbearing potential and females of childbearing potential) while taking study drug;

4. Women who are pregnant or breastfeeding; 5. 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; 6. Known hypersensitivity to any component of the study drug.
Investigational product, dosage, mode of administration, and duration of treatment: Bardoxolone methyl will be administered orally (every other day or once daily) at 10 mg for up to 5 years. The treatment duration may be extended in a future protocol amendment subject to all applicable regulatory and ethics approvals. Dose de-escalation (down to 5 mg) is permitted during the study, if indicated clinically.
Reference therapy, dosage and mode of administration: None.

Criteria for evaluation:

Safety: Results of physical examinations, laboratory results, BNP, NT-ProBNP, vital sign measurements, weight, AEs, and SAEs.

Statistical methods:

Sample size: The aim of this long-term extended access study is primarily to provide continuing treatment to patients with bardoxolone methyl and to assess long-term safety and tolerability, hence no single primary variable has been identified. Patient numbers will be determined by those who have been treatment-compliant and who have previously participated in clinical studies with bardoxolone methyl.

Primary analysis of safety: As the extension is of an open-label design with no comparator group, all statistical analyses will be descriptive. The summary tables will be presented for the overall group of patients, and also split by previous treatment groups (*i.e.,* bardoxolone methyl or placebo) in prior bardoxolone methyl clinical studies.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
6MWD	6-minute walk distance
6MWT	6-minute walk test
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
ATS	American Thoracic Society
BMI	Body mass index
BNP	B-type natriuretic peptide
CFR	Code of Federal Regulations (US)
CK	Creatine kinase
CKD	Chronic kidney disease
CRO	Contract research organization
CTD-PAH	Connective tissue disease-associated pulmonary arterial hypertension
EC	Ethics Committee
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
ICH	International Conference on Harmonization
IKKβ	Inhibitor of nuclear factor kappa β kinase beta subunit
ILD	Interstitial lung disease
INR	International normalized ratio
IRB	Institutional Review Board
Nrf2	Nuclear factor (erythroid-derived 2)-related factor 2
NT-Pro BNP	N-Terminal Pro-Brain Natriuretic Peptide

Abbreviation or Specialist Term	Explanation
NYHA FC	New York Heart Association Functional Classification
PAH	Pulmonary arterial hypertension
PH	Pulmonary hypertension
ROS	Reactive oxygen species
SAE	Serious adverse event
SAP	Statistical analysis plan
TBL	Total bilirubin
ULN	Upper limit of normal
US	United States
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 [ROS]) (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 pulmonary arterial hypertension (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 (PH) (Eba, 2013).

Additionally, an emerging concept in the pathogenesis of PH 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 PH, and glucose intolerance is associated with a decrease in 6-minute walk distance (6MWD) (Pugh, 2011). Pulmonary hypertension patients have decreased adenosine triphosphate (ATP) production (Sutendra, 2014), which results in skeletal muscle dysfunction and impaired functional capacity (Mainguy, 2010; Batt, 2014). Indeed, the skeletal muscle within patients with PH displays a decreased expression of mitochondrial respiration enzymes, defects in mitochondrial oxidative phosphorylation, and impairments in mitochondrial biogenesis (Batt, 2014; Malenfant, 2015). Overall, these defects in skeletal muscle contribute to muscle weakness and fatigue, as well as impaired exercise capacity in patients with PH (Batt, 2014).

Several lines of evidence suggest that Nrf2 activation can increase mitochondrial respiration and biogenesis, in addition to inducing expression of numerous antioxidative genes to counter ROS. Specifically, by increasing the availability and production of reducing equivalents such as nicotinamide adenine dinucleotide and flavin adenine dinucleotide, 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 PH, thereby acutely improving energy production and 6MWD.

Approved PH therapies act to promote vasodilation of pulmonary arteries and through reductions in pulmonary resistance and right-sided cardiac pressure, these therapies have indirect effects on vascular and cardiac remodeling. Additionally, given the degree of parenchymal and vascular fibrosis and remodeling in patients with connective tissue disease-associated PAH (CTD-PAH) and interstitial lung disease (ILD), vasodilation therapies are also minimally effective in treating PH in those 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 PH therapy through improvements in bioenergetics and mitochondrial function that translate to increased muscular function and exercise capacity in patients with PH, including those with CTD-PAH and ILD.

[redacted]

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 significantly improves 6MWD on top of optimal vasodilation background therapies, including 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 CTD. The gains in 6MWD were also sustained through 32 weeks of extended treatment with bardoxolone methyl and

patients with CTD-PAH had similar sustained increases in 6MWD through Week 32. On the basis of these data, Reata expanded the LARIAT protocol (Version 5.0) to include PH patients with ILD, including WHO Group III patients with CTD-associated ILD, idiopathic pulmonary fibrosis, non-specific interstitial pneumonia, and WHO Group V patients with sarcoidosis. Reata has also initiated a Phase 3 study in WHO Group I CTD-PAH patients (402-C-1504, CATALYST, NCT02657356, EudraCT 2016-000196-24) to study the safety and efficacy of bardoxolone methyl in those patients.

5.1. Study Rationale

The established pharmacologic effects of bardoxolone methyl, including the suppression of pathologic NF-κB signaling and inflammation and mitochondrial dysfunction, are directly applicable to the treatment of PH. Despite available therapies, the prognosis for PH remains poor, especially for patients with CTD (Chung, 2014) and ILD. Given the severity of the underlying disease, this study seeks to offer patients who previously participated in clinical studies extended access to bardoxolone methyl until it is available through commercial channels (including reimbursement). For sites in Germany, the trial duration is limited to 5 years following the enrollment of the first patient in Germany. The trial duration may be extended in a future protocol amendment subject to all applicable regulatory and ethics approvals.

For further information, refer to the Investigator's Brochure.

5.2. Clinical Experience with Bardoxolone Methyl

Approximately 1950 individuals have been exposed to bardoxolone methyl at the time of initiation of this study. Sixteen studies have been completed (7 in patients with chronic kidney disease (CKD) who also had type 2 diabetes, 4 in non-CKD indications, and 5 in healthy subjects) and 2 studies are ongoing in patients with PH.

5.2.1. Safety and Tolerability

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

5.2.2. Fluid Overload

Similar to endothelin receptor antagonists 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 a Phase 3 trial (BEACON), which enrolled patients with Stage 4 CKD (eGFR of 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 B-type natriuretic peptide (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 PH (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 (AEs) with bardoxolone methyl in late-stage CKD patients has not been observed in PAH patients.

5.2.3. Transaminase and Gamma-Glutamyl Transpeptidase 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 a large Phase 3 study that enrolled 2185 patients with type 2 diabetes and stage 4 CKD (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 upper limit of normal (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 gamma-glutamyl transpeptidase (GGT), a known Nrf2 target gene. In clinical studies, low level GGT elevations during treatment were common, mild, and typically lasted longer than alanine aminotransferase (ALT)/aspartate aminotransferase (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.

5.2.4. Muscle Spasms

Muscle spasm was the most frequently reported AE in clinical studies 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, blood urea nitrogen, 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).

5.2.5. 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 AEs 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 AEs.

5.2.6. Hypomagnesaemia

Hypomagnesaemia has not been reported in PAH patients to date, but was reported as an AE for 15.5% of patients with CKD who also had type 2 diabetes who received bardoxolone methyl. The AE 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 AEs or cardiac AEs, 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. Primary Objectives

To provide continuing treatment with bardoxolone methyl as part of this extended access program while collecting ongoing safety and tolerability data of bardoxolone methyl.

6.2. Primary Safety Endpoint:

Frequency, intensity, and relationship to study drug of adverse events (AEs) and serious adverse events (SAEs), and change from baseline in the following assessments: physical examinations, vital sign measurements, BNP, N-terminal pro-brain natriuretic peptide (NT-proBNP), and weight.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This extended access study will assess the long-term safety and tolerability of bardoxolone methyl in qualified patients with PH who previously participated in controlled clinical studies with bardoxolone methyl.

Qualified patients will start dosing at 10 mg of bardoxolone methyl every other day, then begin once daily dosing at Week 4 (unless contraindicated clinically) and continue the drug for up to 5 years or until patient withdrawal, whichever is sooner. The treatment duration may be extended in a future protocol amendment subject to all applicable regulatory and ethics approvals. Dose de-escalation (down to 5 mg) is permitted during the study if indicated clinically. Refer to Section 7.3.1 for additional details on dose de-escalation.

All patients in the study will follow the same visit and assessment schedule. Patients will be scheduled to be assessed in person during treatment at Day 1, Week 2, Week 4, Week 6, Week 8, Week 24, and every 24 weeks thereafter. Patients will also be assessed by telephone contact on Days 3, 10, 21, 31, and 38. Day 1 for this extended access study should occur on the same day as the last visit in the controlled clinical study. Patient status should be carefully monitored by the investigator during the first 8 weeks of study treatment. Assessments required for both the last visit in the controlled study and Day 1 for this study should only be completed once.

Patients from the CATALYST study:

Day 1 of this extended access study will coincide with the Week 28 follow-up visit for patients from CATALYST (402-C-1504, NCT02657356, EudraCT 2016-000196-24). If this extended access program is not yet open for enrollment at the time of a patient's Week 28 visit, the Day 1 visit (*i.e.*, enrollment) must occur within 30 days of site activation. Exceptions allowing CATALYST patients who have completed 24 weeks of treatment to schedule their follow-up assessments prior to Week 28 and still be considered eligible for this open-label study should be discussed with the Chief Medical Officer at Reata, or designee, and will be considered on a case-by-case basis.

Patients from the LARIAT study:

Day 1 of this extended access study will coincide with the End-of-Treatment visit for patients from LARIAT (402-C-1302, NCT02036970).

7.2. Number of Patients

Patient numbers will be determined by those who have been treatment-compliant and who have previously participated in clinical studies with bardoxolone methyl.

7.3. Treatment Assignment

All patients will receive bardoxolone methyl in this study.

7.3.1. Dose Escalation and Dose De-Escalation

Patients will start dosing at 10 mg of bardoxolone methyl every other day, then begin once daily dosing at Week 4 unless contraindicated clinically. The investigator should discuss any reasons for not dose-escalating to once daily dosing at Week 4 with the medical monitor.

Dose de-escalation is permitted during the study and the investigator may choose to decrease the patient's dose to 5 mg if clinically indicated. Reasons for dose de-escalation should be discussed with the medical monitor prior to changing dose. Once a patient's dose has been decreased to 5 mg, they cannot dose-escalate back to 10 mg of bardoxolone methyl.

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

7.4. Criteria for Study Termination

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 drugs will be discontinued and the investigator will be responsible for securing any alternative therapy to be administered, as appropriate.

7.5. Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of Good Clinical Practice (GCP), protocol, or contractual agreement with Sponsor or the site is unable to ensure adequate performance of the study.

7.6. Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Sites

In the event that the Sponsor, an institutional review board (IRB)/ethics committee (EC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor.

7.7. Schedule of Assessments

Table 3 lists the overall schedule of assessments for the study.

Table 3: Schedule of Assessments

Assessment \ Study Week (Day)	Day 1[a]	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	Week 8 Day 56±3	Week 24±3, Every 24 Weeks	End of Study Visit[b]
Informed consent	X												
Inclusion/Exclusion	X												
Prior and Concomitant medications	X[c]	X	X	X	X	X	X	X	X	X	X	X	X
Current PAH background medications	X[c]	X	X	X	X	X	X	X	X	X	X	X	X
Weight at home	X	X	X	X	X	X	X	X	X	X	X		
Weight in clinic	X[c]		X		X		X			X	X	X	X
Vital sign measurements	X[c]		X		X		X			X	X	X	X
Physical examination	X[c]		X		X		X			X	X	X	X
Pregnancy test[d]	X[c]											X	
Dispense study drug	X						X					X	
Collect study drug							X					X	X
Telephone contact		X		X		X		X	X				
Adverse event collection	X[e]	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistries[f]	X[c]		X		X		X			X	X	X	X
BNP and/or NT-Pro BNP	X[c]		X		X		X			X	X	X	X
6-min walk test	X[c]											X	X
Dyspnea and fatigue[g]	X[c]											X	X
WHO functional class	X[c]											X	X

[a] On Day 1, all procedures should be performed before study drug administration for patients who are treatment-compliant and have previously participated in clinical studies with bardoxolone methyl.

[b] After the Week 24 visit, patients will continue to be assessed in person every 24 weeks. The End of Study visit should occur within 30 days after the patient receives their final dose of study medication under this protocol. Patients who will be discontinued from the study prior to the completion of the study must also complete all End-of-Study assessments.

[c] Day 1 assessments should be performed as part of End-of-Treatment or Follow-up visit procedures from a prior study with bardoxolone methyl.

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

[e] AE assessments on Day 1 should be performed following study drug administration.
[f] Clinical chemistries will be analyzed locally.
[g] Dyspnea and fatigue must be assessed prior to beginning and immediately following completion of the 6MWT using the Borg scale.

Abbreviations: PAH, pulmonary arterial hypertension; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide; WHO, World Health Organization; AE, adverse event; 6MWT, 6-minute walk test.

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Patient Inclusion Criteria

Main criteria for inclusion:

1. Treatment-compliant patients who are participating in qualifying ongoing studies (CATALYST, EudraCT 2016-000196-24; LARIAT, EudraCT 2016-004793-17) and who have completed required End-of-Treatment and/or Follow-up visits in one of these prior clinical studies with bardoxolone methyl and who, according to the assessment of the investigator, have a potential positive benefit-risk assessment for participating in the trial.
2. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study prior to initiation of any protocol-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;
2. Patients who have an ongoing serious adverse event (SAE) from a clinical study that is assessed by the investigator as related to bardoxolone methyl;
3. Unwilling to practice acceptable methods of birth control (both males who have partners of childbearing potential and females of childbearing potential) while taking study drug;
4. Women who are pregnant or breastfeeding;
5. 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;
6. Known hypersensitivity to any component of the study drug.

8.3. 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).

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

- Occurrence of an AE or change in medical status that will lead 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;
- Premature termination or suspension of an investigational site;
- Loss to follow-up;
- Death;
- Withdrawal of consent.

Patients must discontinue study drug if any of the following occur.

- ALT or AST > 8X ULN;
- ALT or AST > 5X ULN for more than 2 weeks;
- ALT or AST > 3X ULN and (total bilirubin > 2X ULN or International Normalized Ratio [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 discontinue from the study will be asked to complete the End-of-Study procedures noted in Table 3.

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. Laboratory data, as well as BNP and/or NT-proBNP, will also be used to monitor fluid status.

Additionally, patients will be monitored for rapid weight gain suggestive of fluid overload. Patients will be given a Sponsor-provided scale to use at home to monitor their weights daily during the first 8 weeks of the treatment period. Patients who experience a 5-pound (2.3 kilogram) or greater increase in weight since their Day 1 weight during the first 8 weeks of the treatment period will be instructed to stop taking their study medication immediately and return to the clinic for an unscheduled physical examination and laboratory assessment by the investigator. Patients may not restart their study medication until the investigator has completed and documented an assessment of fluid overload.

Investigators should 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 will be 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)

Transaminases should be monitored following patient's standard of care. Nearly all instances of elevated transaminases are expected to be asymptomatic. Transaminase levels (as well as total bilirubin [TBL], GGT, alkaline phosphatase, and INR) will be checked within 48 to 72 hours during an unscheduled visit if the following occurs:

- ALT or AST levels > 3X ULN.

Testing will be repeated every 72 to 96 hours until transaminase levels are below 3X the ULN for at least one week or until the patient withdraws consent.

Study drug administration will be permanently discontinued 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, magnetic resonance imaging) 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 as part of patient's standard of care 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 (evaluated as part of patient's standard of care), 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 AEs are typically mild and reversible within a few weeks after treatment initiation. If symptoms will not resolve, dose de-escalation, with consultation of the medical monitor, may be necessary.

9.2. Description of Study Drug

Bardoxolone methyl (RTA 402) drug product information is shown in Table 4.

Table 4: Bardoxolone Methyl Drug Product Information

Description	Bardoxolone methyl capsule (5 mg, 10 mg)
Ingredients	Bardoxolone methyl Methacrylic Acid – Ethyl Acrylate Copolymer [redacted] Type A Silicified Microcrystalline Cellulose Hydroxypropyl Methylcellulose Lactose Monohydrate Sodium Lauryl Sulfate Colloidal Silicon Dioxide Magnesium Stearate Gelatin capsules Titanium Dioxide [redacted]
Route of Administration	Oral

9.3. Concomitant Medications

9.3.1. Excluded Medications

No other investigational drug or device should be taken as part of an interventional study during the conduct of this study.

Patients who take investigational drug or device 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

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

Refer to Section 9.10.15 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 electronic case report form (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.

9.5. Randomization

Not applicable.

9.6. Blinding

Not applicable.

9.7. Unscheduled Visits

Unscheduled visits are allowed for the following reasons:

- Assessment of weight gain per Section 9.1.1;
- Management of an AE or SAE;
- 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 AEs, concomitant medications and vital signs. 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

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 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.

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);
- 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-Study 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 an SAE:

- 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. A single dose reduction (from 10 mg to 5 mg) is permitted if clinically indicated to manage tolerability issues. Once a patient's dose has been reduced, that dose must

be maintained. 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.

9.10.3. 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.

9.10.4. 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 US Food and Drug Administration (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.

9.10.5. Weight and Body Mass Index

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. Patients will use Sponsor-provided scales to measure weight at home. 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.

9.10.6. 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.

9.10.7. 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. Clinically significant findings at Day 1 must be recorded as medical history. Following the examination on Day 1, new or changed physical examination findings meeting the criteria for an adverse event must be recorded as an adverse event. If possible, the same individual should perform each physical examination on a patient during the study.

9.10.8. 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.

9.10.9. Study Drug Administration

Patients should self-administer one capsule orally, once a day, preferably in the morning, as indicated in Table 3. 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.

9.10.10. 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 1 or more treatment kits at Day 1, Week 4, Week 24, and every 24 weeks thereafter for the duration of the study. Dispensed treatment kits from each visit should be returned to the site for collection at the subsequent visit.

9.10.11. 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 AEs 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.

9.10.12. 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.

9.10.13. Clinical Chemistry

Samples will be collected for clinical chemistry analyses as indicated in Table 3. Clinical chemistries will be analyzed locally and should include those routinely monitored per patient's standard of care.

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

Samples will be collected for NT-Pro BNP and/or 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 1 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.

9.10.15. 6-Minute Walk Test

A 6-minute walk test (6MWT) will be performed by the 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.

Patients will rate their dyspnea and overall fatigue using the Borg scale (2004 version, provided in Section 21, Appendix 3) prior to beginning and immediately following completion of each 6MWT as indicated in Table 3.

The assessor of the 6MWT must not provide the patient with the results of the assessment once complete. A patient should wear the same or similar shoes for all 6MWTs. Additionally, if a patient uses a walking aid 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. 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.

9.10.16. WHO/NYHA Functional Class Assessment

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

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

Bardoxolone methyl capsules, 5 mg and 10 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 one 30-cc (5-mg capsules, 30 count), one 60-cc (5-mg capsules, 90 count), or one 100-cc (10-mg capsules, 90 count) high-density polyethylene bottle. Each bottle will utilize foil induction-seal liners and a child-resistant closure. Each bottle of study drug will contain 30 or 90 capsules of 5 mg or 10 mg strength bardoxolone methyl. 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 identification number;
- Protocol 402-C-1602;
- 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 bottle containing this and other information as well. Additionally, labeling in the relevant local languages for investigational medicinal product 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°C to 25°C (68°F to 77°F), with brief excursions allowed to 15°C to 30°C (59°F to 86°F).

10.4. Study Drug Administration

Please refer to Section 9.10.9 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 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 will complete all safety assessments. Safety parameters will include vital sign measurements, physical examination results, AEs, SAEs, weight, and assessment of BNP and/or NT-Pro BNP.

11.2. Adverse and Serious Adverse Events

11.2.1. Definition of Adverse Events

11.2.1.1. Adverse Event

An 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

An 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 receives the first dose of study drug 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, nondirected 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 that are monitored per patient's standard of care, physical examination findings, 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) in a previous study with bardoxolone methyl should be documented as medical history in a previous study with bardoxolone methyl. After the first dose, documentation of AEs shall continue until 30 days following administration of the final dose of study medication under this protocol (*i.e.,* through the End-of-Treatment visit), regardless of the relationship of the AE to study drug. Information to be collected will include 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 will 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) will be 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 shall be recorded as an AE. Investigators shall ensure that the AE term recorded captures the change in the condition (*e.g.,* "worsening of…"). Any improvement in condition shall be documented per Section 9.10.7.

Each AE shall be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory test values) or symptoms shall NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) shall be recorded as an AE(s). Changes in laboratory test values will only be 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 will be the result of pathology for which there will be an overall diagnosis (*e.g.,* increased creatinine levels in renal failure), only the diagnosis shall be reported as an AE.

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

11.7. Reporting Serious Adverse Events

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

To report the SAE, the investigator will complete the SAE form in the clinical database and send to [redacted] (fax numbers listed in Table 5) within 24 hours of awareness. If the clinical database is down for any reason, the manual SAE forms will be utilized; however sites are responsible for ensuring the information on the manual SAE forms is entered into the clinical database once available.

Table 5: SAE Reporting Contact Information

[redacted] Non-North American sites will use access codes specific to their country. Contact information for non-North American sites for SAE reporting will be provided by the clinical team directly to the sites.

For questions regarding SAE reporting, contact your study manager, monitor, or [redacted]

Follow-Up Reports

The investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient 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.,* patient discharge summary or autopsy reports). 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 IRB or EC, as appropriate.

Principal investigators will be 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 AEs 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;
- Lightheadedness/dizziness;
- 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

The aim of this long-term extended access study is primarily to provide continuing treatment to patients with bardoxolone methyl and to assess long-term safety and tolerability, hence no single primary variable has been identified. Patient numbers will be determined by those who have been treatment-compliant and who have previously participated in clinical studies with bardoxolone methyl.

12.2. Study Variables

12.2.1. Safety Variables

The safety variables will include results of physical examinations, laboratory test results (BNP and NT-Pro BNP), vital sign measurements, weight, AEs, and SAEs.

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 Safety

As the extension is of an open-label design with no comparator group, all statistical analyses will be descriptive. Patients will be included in these analyses if they are included in the safety analysis and have both baseline and post-baseline data available for the variable being analyzed.

The summary tables will be presented for the overall group of patients, and also split by previous treatment groups in prior bardoxolone methyl clinical studies.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study-Specific Committees

No steering committee, data safety monitoring committee, adjudication committee, or clinical endpoint committee will be used in this study.

13.2. Study Monitoring

The study site will be monitored remotely by the CRO periodically during the study to ensure that all aspects of the protocol will be followed and will include an electronic data collection which has a set of automatic data checks with data queries for programmed data collection. There will be monitoring of study site by telephone to ensure that the drug supplies have been provided and protocol instructions are well understood and applied.

The Sponsor or designee will monitor all aspects of the study for compliance with applicable government regulation with respect to the International Council for Harmonisation (ICH) guideline E6(R2): Good Clinical Practice: Consolidated Guideline and current standard operating procedures.

13.3. 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 will agree to allow the Sponsor, representatives of the Sponsor, the FDA, and other relevant regulatory authorities access to all study records.

The principal investigator shall promptly notify the Sponsor or designee of any audits scheduled by any regulatory authorities and shall 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(R2) 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 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. Continuous monitoring of the benefits and risks of bardoxolone methyl is performed by Reata in reviewing data from all ongoing and prior trials with bardoxolone methyl and by the safety monitoring committees that oversee safety for the ongoing placebo-controlled Phase 2 and Phase 3 trials (CATALYST, EudraCT 2016-000196-24; LARIAT, EudraCT 2016-004793-17).

The principal investigator agrees to conduct the study in accordance with the International Conference on Harmonization (ICH) for Guidance for Industry on GCP ICH E6(R2) [https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf] and the principles of the Declaration of Helsinki [https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/]. 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 US Investigational New Drug Application, a signed informed consent form, in compliance with Title 21 of the US CFR Part 50, will be obtained from each patient before the patient enters the study. For sites outside of the US, the signed consent will be obtained in accord with local regulations, ICH E6 (R2), 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 will be used to capture data electronically for all enrolled 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(1):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(1):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 (Hoboken). 2014;66(3):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 U S A. 2005;102(12):4584-9.

Eba S, Hoshikawa Y, Moriguchi T, et al. The nuclear factor erythroid 2-related factor 2 activator oltipraz attenuates chronic hypoxia-induced cardiopulmonary alterations in mice. Am J Respir Cell Mol Biol. 2013;49(2):324-33.

Galiè N, Hoeper MM, Humbert M, et al. 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(4):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 DF, Kuo HP, Liu M, et al. KEAP1 E3 ligase-mediated downregulation of NF-kB signaling by targeting IKKbeta. Mol Cell. 2009;36(1):131-40.

Ludtmann MH, Angelova PR, Zhang Y, et al. Nrf2 impacts the efficiency of mitochondrial fatty acid oxidation. Biochem J. 2014;457(3):415-24.

Mainguy V, Maltais F, Saey D, et al. Peripheral muscle dysfunction in idiopathic pulmonary hypertension. Thorax. 2010;65(2):113-7.

Malenfant S, Potus F, Fournier F, et al. Skeletal muscle proteomic signature and metabolic impairment in pulmonary hypertension. J Mol Med (Berl). 2015;93(5):573-84.

Osburn WOand, Kensler TW. Nrf2 signaling: An adaptive response pathway for protection against environmental toxic insults. Mutat Res. 2008;659(1-2):31-9.

Price L, Caramori G, Dorfmuller P, et al. Endothelial cell NF-kB activation is increased in human idiopathic PAH. Thorax. 2010;65(4):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(8):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 PK, Reddy VT, 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(52):40581-92.

Sutendra G, Michelakis ED. The metabolic basis of pulmonary arterial hypertension. Cell Metab. 2014;19(4):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(3):952-8.

Wu QQ, Wang Y, Senitko M, et al. Bardoxolone methyl (BARD) ameliorates ischemic AKI and increases expression of protective genes Nrf2, PPARγ, and HO-1. Am J Physiol Renal Physiol. 2011;300(5):F1180-F1192.

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.

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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 st 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. though 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. APPENDIX 3: BORG CR10 SCALE