EXPEDITE: A 16-Week, Multicenter, Open-label Study of Remodulin Induction Followed by Orenitram Optimization in Subjects with Pulmonary Arterial Hypertension

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CONFIDENTIAL

UNITED THERAPEUTICS CORPORATION

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INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "EXPEDITE: A 16-Week, Multicenter, Open-label Study of Remodulin Induction Followed by Orenitram Optimization in Subjects with Pulmonary Arterial Hypertension," Amendment 3 dated 24 June 2019 and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice and applicable Food and Drug Administration regulations/guidelines set forth in 21 Code of Federal Regulations Parts 50, 54, 56, and 312 and any local regulations per country.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of United Therapeutics Corp.

I also have read the current Clinical Investigators' Brochures for Remodulin (treprostinil) Injection and Orenitram (treprostinil) Extended Release Tablets and acknowledge that review of the information contained in the Clinical Investigators' Brochures is a requirement for Investigators before using Remodulin and Orenitram in a clinical study.

This protocol has been received for information only and must not be implemented before all necessary regulatory agency and Ethics Committee/Institutional Review Board approval documents have been obtained.

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

PROTOCOL SYNOPSIS

Title	EXPEDITE: A 16-Week, Multicenter, Open-label Study of Remodulin Induction Followed by Orenitram Optimization in Subjects with Pulmonary Arterial Hypertension
Study Phase	4
Indication	Pulmonary arterial hypertension (PAH)
Primary Objective	The primary objective of the study is to evaluate the dose of Orenitram® (treprostinil) Extended Release Tablets achieved at 16 weeks after induction therapy with Remodulin® (treprostinil) Injection in PAH patients. The primary endpoint is: The percentage of subjects achieving an Orenitram dose of 4 mg 3 times daily (TID) (or a total daily dose of 12 mg) or higher at Week 16 (or a dose of 0.057 mg/kg TID [or a total daily dose of 0.171 mg/kg] or greater for subjects <70 kg).
Secondary Objective(s)	To assess the effect of Orenitram treatment at 16 weeks after induction therapy with Remodulin on the following: 1. Clinical response: • 6-Minute Walk Distance (6MWD) • Borg dyspnea score • World Health Organization (WHO) Functional Classification (FC) • Serum N-terminal pro-brain natriuretic peptide (NT-proBNP) • Echocardiogram • PAH symptom score • Health-related quality of life (emPHasis-10) • Treatment Satisfaction Questionnaire for Medication (TSQM) scores • Percentage of subjects that improve in each of the following individual 4 clinical parameters at Week 16 (6MWD, NT-proBNP, WHO FC, right atrial area) to a lower risk stratum, as defined by the 2015 European Society of Cardiology guidelines, compared to Baseline • Percentage of subjects that meet each of the following 4 individual clinical parameters at Week 16 in the low risk category, as defined by 2015 European Society of Cardiology guidelines: 6MWD >440 meters, serum NT-proBNP <300 ng/L, WHO FC I or II, and right atrial area <18 cm^2

	• Percentage of subjects that either achieve an Orenitram dose of 4 mg TID (or a total daily dose of 12 mg) or higher at Week 16 (or a dose of 0.057 mg/kg TID [or a total daily dose of 0.171 mg/kg] or greater for subjects <70 kg) or the percentage of subjects that achieve an Orenitram dose ≥2 mg TID and <4 mg TID (or a total daily dose ≥6 mg and <12 mg) at Week 16, with at least 2 of the following 3 clinical parameters at Week 16: 6MWD increase by ≥10% or ≥30 meters from Baseline, serum NT-proBNP reduction >30% from Baseline, or WHO FC I or II • The percentage of subjects that successfully transitioned to Orenitram at any dose and were maintained on therapy at Week 16 2. Safety and tolerability • Adverse events • AE Bothersome Survey • Clinical laboratory parameters • Vital signs
Exploratory Objectives	Optional evaluation of pharmacogenomics (genetic/ribonucleic acid [RNA]) and biomarker testing (specific targets to be determined) at Baseline, the Transition Visit, and Week 16.
Study Design	16-week, multicenter, open-label, uncontrolled study in subjects with PAH
Sample Size	Approximately 30 evaluable subjects will be enrolled
Summary of Subject Eligibility Criteria	Eligible subjects must be aged 18 to 75 years, have a confirmed diagnosis of WHO Group 1 pulmonary hypertension by right heart catheterization, have WHO FC II or III symptoms at Baseline, and have a Baseline 6MWD of >250 meters. Subjects who are either not receiving PAH-targeted therapy or are currently being treated with 1 or 2 Food and Drug Administration (FDA)-approved oral therapies consisting of an endothelin receptor antagonist (ERA) and/or either a phosphodiesterase type-5 inhibitor (PDE5-I) or a soluble guanylate cyclase (sGC) stimulator for ≥45 days, and on a stable dose for ≥30 days prior to the Baseline Visit. Subjects who have received a prostacyclin-class therapy within 28 days of Baseline and those with a Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) 2.0 risk score of 10 or greater are ineligible for this study.

Drug Dosage and Formulation	Remodulin will be provided in vial strengths of 1 mg/mL, 2.5 mg/mL, 5 mg/mL, and 10 mg/mL. Subjects will be initiated on subcutaneous (SC) or intravenous (IV) Remodulin at 2 ng/kg/min in the inpatient or outpatient setting and should be optimized on Remodulin therapy prior to transition to Orenitram; a dose should be achieved that improves the symptoms of PAH while minimizing excessive pharmacologic effects of Remodulin. There is no maximum Remodulin dose during the study. Subjects may transition at Weeks 2, 4, or 8 if they have achieved a minimum Remodulin dose of 20 ng/kg/min and the Investigator deems the subject suitable for transition. All subjects still on Remodulin at Week 8 should transition to Orenitram regardless of their Remodulin dose unless the Investigator deems them unsuitable for transition to Orenitram due to significant signs or symptoms of PAH or any other serious safety concerns. Orenitram will be provided in the extended-release tablet strengths of 0.125 mg, 0.25 mg, 1 mg, 2.5 mg, and 5 mg. Subjects will be instructed to take the appropriate number of 0.125 mg, 0.25 mg, 1 mg, 2.5 mg, and 5 mg tablets based upon their Remodulin dose and the transition schedule chosen by their healthcare provider. There is no maximum Orenitram dose during the study.
Control Group	None
Route of Administration	Remodulin: SC or IV Orenitram: oral
Procedures	*Study Visit Schedule* • Subjects will be assessed at Screening, Baseline, Weeks 2, 4, 8, 12, and 16. Subjects will also return to the study site 7 to 14 days after beginning transition to Orenitram (ie, Post Transition Visit). • Subjects will be assessed during Screening and Baseline to determine eligibility for the study. • At Baseline, subjects will be initiated on SC or IV Remodulin at 2 ng/kg/min. • Subjects should be optimized on Remodulin therapy prior to transition to Orenitram; a dose should be achieved that improves the symptoms of PAH while minimizing excessive pharmacologic effects of Remodulin.

	• Subjects may transition at Weeks 2, 4, or 8 if they have achieved a minimum Remodulin dose of 20 ng/kg/min and the Investigator deems the subject suitable for transition. • Transition may be reversed or stopped if the Investigator feels it is necessary for subject safety. • Subjects will transition from Remodulin to Orenitram over the course of 1 to 21 days in an inpatient or outpatient setting. • Following transition, Orenitram titration should continue through Week 16 to reach the maximum tolerated dose. *Efficacy Assessments*: Orenitram dose achieved, exercise capacity (6MWD and Borg dyspnea score), WHO FC, NT-proBNP, health-related quality of life (emPHasis-10), TSQM scores, PAH symptom score, echocardiograms *Safety and Tolerability Assessments*: Adverse events, clinical laboratory evaluations, vital signs *Optional Assessments:* Pharmacogenomic (genetic/RNA) and biomarker testing
Statistical Considerations	Approximately 30 evaluable subjects were set for feasibility and to ensure a reasonable dataset to evaluate the Orenitram dose achieved, and the clinical response, safety, and tolerability of Orenitram after induction therapy with Remodulin. No formal sample size computation was performed with respect to the study endpoints.
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TABLE OF CONTENTS

Table of In-Text Tables

LIST OF ABBREVIATIONS

Abbreviation	Definition
6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
AE	Adverse event
BID	Twice daily
C_{max}	Maximal drug concentration
CYP	Cytochrome P450 enzyme
ECHO	Echocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ERA	Endothelin receptor antagonist
FC	Functional Classification
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDS	Global Drug Safety
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
NT-proBNP	N-Terminal pro-brain natriuretic peptide
PAH	Pulmonary arterial hypertension
PAWP	Pulmonary artery wedge pressure
PK	Pharmacokinetic(s)
PDE5-I	Phosphodiesterase type-5 inhibitor
PVR	Pulmonary vascular resistance
REVEAL	Registry to Evaluate Early and Long-Term PAH Disease Management
RHC	Right heart catheterization
RNA	Ribonucleic acid
SAE	Serious adverse event
RV	Right ventricular
SC	Subcutaneous(ly)
SD	Standard deviation
sGC	Soluble guanylate cyclase
SR	Sustained release
TDD	Total daily dose
TID	3 times daily
TSQM	Treatment Satisfaction Questionnaire for Medication
US	United States

USPI	United States Prescribing Information
WHO	World Health Organization

1 BACKGROUND AND RATIONALE

1.1 DEFINITION OF CLINICAL PROBLEM

Pulmonary arterial hypertension (PAH), which is defined as an elevation in pulmonary arterial pressure and pulmonary vascular resistance (PVR), is a severe hemodynamic abnormality associated with a variety of diseases and syndromes. Elevations in PVR cause an increase in right ventricular (RV) afterload, impairing RV function and ultimately leading to progressive limiting symptoms and death.

Orenitram® was approved by the United States Food and Drug Administration (FDA) in 2013 for PAH (World Health Organization [WHO] Group 1) to improve exercise capacity. Orenitram dosing is individualized to effect and tolerability, thus it is important to achieve optimal treprostinil doses as quickly as possible. Higher doses of treprostinil correlate with improved exercise capacity, and there are data to suggest that Remodulin® doses of ≥40 ng/kg/min may improve long-term survival (Simonneau 2002, Hiremath 2010, Tapson 2013, Jing 2013, Benza 2011).

Commercial data, as well as anecdotal reports from health care providers, suggest that adverse events (AEs) are a common cause of Orenitram discontinuation early on in the course of treatment. This is reflected by the median total daily dose (TDD) of Orenitram at 6 months of 7.5 mg (Balasubramanian 2017). Results from a recent clinical study suggest PAH patients previously receiving Remodulin may tolerate significantly higher doses of Orenitram as compared to patients without prior Remodulin exposure (Chakinala 2017). Additionally, several open-label and controlled studies have demonstrated the safety and efficacy of aggressive Remodulin titration (Sitbon 2007, Hansen 2014, Grünig 2016).

The EXPEDITE study will evaluate the Orenitram doses that PAH patients achieve after treprostinil induction using a short-term course of Remodulin.

1.2 TREPROSTINIL BACKGROUND

1.2.1 General Pharmacology

Treprostinil, [[(1R,2R,3aS,9aS) 2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H benz [f]inden-5-yl]oxy]acetic acid, is a chemically stable tricyclic analogue of prostacyclin. The pharmacology of treprostinil has been extensively characterized in well-established models, all confirming the suitability of the drug to treat PAH following the parenteral (as treprostinil sodium), inhaled (as treprostinil sodium), or oral (as treprostinil diolamine) routes of administration. A detailed description of preclinical and clinical information of treprostinil for injection is provided in the Remodulin Investigator's Brochure.

The major pharmacological actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. In vitro, treprostinil induced concentration-dependent relaxation of rabbit-isolated precontracted mesenteric arteries, and inhibition of adenosine diphosphate-induced platelet aggregation in human and rat platelet-rich plasma. In animals, the vasodilatory effects of treprostinil reduce right and left ventricular afterload, thereby increasing cardiac output and stroke volume. Prostacyclins lower pulmonary artery pressure, increase cardiac output without affecting the heart rate, improve systemic oxygen transport, as well as possibly reversing pulmonary artery remodeling. There is also increasing evidence that the ability to block the proliferation of pulmonary artery smooth muscle cells may contribute, along with vasodilation, to the therapeutic effects of prostacyclins in the treatment of PAH. The mechanism of action is therefore likely to be multifactorial.

Treprostinil diolamine (UT-15C sustained release [SR]), hereinafter referred to as oral treprostinil, was selected from a series of treprostinil salts based on critical physicochemical characteristics (eg, solubility, hygroscopicity, melting point) with a goal of delivering treprostinil by the oral route as an SR dosage form. In solution, both treprostinil sodium and treprostinil diolamine are disassociated from their respective salt counter-ions and exist as the freely ionized form of treprostinil. As a result, the biologically active form present in the bloodstream is identical, irrespective of the counter-ion used in the formulation.

Additional nonclinical studies have shown that the observed pharmacological profile of oral treprostinil reflects the activity of the parent molecule, treprostinil, and that the contribution to that profile of any known metabolite that would be formed in vivo would be minimal.

1.2.2 General Toxicology

Oral treprostinil is a novel salt form of Remodulin (treprostinil) Injection and Tyvaso® (treprostinil) Inhalation Solution, which are approved in the United States (US) to treat subjects with PAH. In addition to the nonclinical studies conducted with oral treprostinil, an extensive amount of pharmacology, pharmacokinetic (PK), and toxicology information on treprostinil sodium is available from Remodulin and Tyvaso development.

During the development of Remodulin, treprostinil sodium was administered subcutaneously (SC) and/or intravenously (IV) in acute toxicity studies, repeat-dose toxicity studies, reproductive toxicity studies, and genotoxicity studies, and has a well-defined clinical safety profile. Treprostinil sodium was administered via continuous infusion to rats and dogs in toxicity studies for up to 6 months, which supported the safety of chronic administration of Remodulin to subjects.

In addition to the extensive toxicology data with treprostinil sodium, the toxicity and toxicokinetic profiles of oral treprostinil have been evaluated in acute and repeat-dose oral toxicity studies of up to 13 weeks duration in rodents and up to 9 months duration in dogs. Oral treprostinil has also been evaluated in reproductive developmental toxicity studies in pregnant rats and rabbits and in an in vivo rat micronucleus assay.

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, and genotoxicity. A comprehensive description of oral treprostinil, including the pharmacology, toxicology, and clinical studies completed to date, may be found in the current Orenitram Investigator's Brochure.

Segment I, II, and III studies have been completed in rats, and a Segment II study has been completed in rabbits. No adverse effects for fetal viability/growth and fetal development (teratogenicity) were seen in rats at or below 20 mg/kg/day or in rabbits at or below

0.5 mg/kg/day. At high doses, teratogenic effects of oral treprostinil were observed in rabbits. Findings included increased fetal incidence of external, soft tissue, and skeletal malformations. Initial parent generation female rats receiving 10 mg/kg/day had decreased food consumption and body weights during gestation, increased duration of gestation, slight decreases in the viability and number of pups per litter, and pups with decreased mean neonatal body weights.

A 6-month carcinogenicity study in mice with oral treprostinil administered at daily oral doses of 3, 7.5, and 15 mg/kg in females and 5, 10, and 20 mg/kg in males for 26 weeks did not demonstrate increases in the incidence of neoplastic lesions. A 2-year rat carcinogenicity study demonstrated that daily administration of oral treprostinil does not have carcinogenic potential.

A Good Laboratory Practices, cardiovascular, safety pharmacology study to evaluate diolamine effects, independent of treprostinil, on cardiovascular function in telemetered dogs was conducted. Data support that oral administration of diolamine at doses up to 2 mg/kg/dose twice daily (BID; 4 mg/kg/day) to male beagle dogs was not associated with any definitive changes in arterial pressure, heart rate, or electrocardiogram parameters. In addition, no abnormal clinical signs were noted in the animals dosed with the vehicle or with any of the doses of diolamine.

1.2.3 Clinical Pharmacology

The most frequent AEs associated with Remodulin in clinical studies of subjects with PAH were related to the pharmacological properties of Remodulin and were generally not serious. These prostacyclin-related AEs included diarrhea, headache, and nausea. Remodulin has not been associated with any significant changes in laboratory parameters or end-organ toxicity. The safety profile noted in an open-label extension study, with much longer durations of exposure and a larger, more diverse subject population, was consistent with the profile noted in the controlled studies. To date, over 20,000 patients have been exposed to Remodulin. This number includes subjects who have received single administration to subjects receiving continuous infusion for greater than 15 years.

Oral treprostinil has been administered to approximately 2344 subjects in Phase 1 to 3 clinical studies. Oral treprostinil doses of up to 3 mg BID have been administered to healthy volunteers, and subjects with PAH have received up to 27.5 mg 3 times daily (TID) in an open-label extension study. The average exposure is approximately 2 years; the longest exposure is approximately 8 years.

The absolute bioavailability of the oral treprostinil 1 mg tablet is 17.6%. Following administration, treprostinil diolamine is widely distributed. Treprostinil is approximately 96% protein bound, with no effect on warfarin or digoxin displacement. Pharmacokinetic data (area under the plasma concentration-time curve) indicate that Day 1 PK data are predictive of Day 13, and linearity was observed in plasma exposure comparing 1-mg and 2-mg doses in healthy volunteers. Food, particularly a high fat, high calorie meal, has been observed to increase absorption and prolong the systemic exposure to treprostinil, contributing to the desired PK profile. Consistent with in vitro studies, clinical studies assessing the impact of induction and inhibition of the cytochrome P450 enzyme (CYP) 2C8 and CYP 2C9 metabolic pathways on oral treprostinil indicate that CYP 2C8 appears to be of major importance and CYP 2C9 of minor importance to in vivo metabolism of oral treprostinil in humans.

To date, the majority of oral treprostinil studies have been conducted with BID dosing. In an attempt to understand the PK of TID dosing, a study was conducted in healthy volunteers. In this open-label, single-center study, 19 healthy subjects received 0.5 mg TID for 7 days. Nineteen subjects (10 females and 9 males) with a mean age of 35.2 years (range: 20 to 54 years) were enrolled. On Day 1, the mean maximal drug concentration (C_{max}) ± standard deviation (SD) of treprostinil was 0.574±0.22 ng/mL, which occurred at a median time of 4 hours (range: 2 to 6 hours). In comparison, the Day 8 mean C_{max} (±SD) was 0.615±0.32 ng/mL and occurred at a median time of 4 hours (range: 1 to 6 hours).

On Day 7, the mean C_{max} (±SD) was 0.810±0.491 ng/mL and occurred at a median time of 14 hours (range: 6 to 20 hours) following the morning dose. This indicated that maximum concentration during a daily interval at steady state occurs after the evening (or third) dose of the day. Mean trough plasma concentrations prior to the morning dose on Days 5, 6, 7, and 8

were 0.049, 0.049, 0.050, and 0.053 ng/mL, respectively. Mean trough concentrations prior to the evening dose on Days 4, 5, 6, and 7 were 0.487, 0.396, 0.437, and 0.353 ng/mL, respectively.

Sixteen AEs occurred in 7 subjects and primarily included known prostacyclin class effect-related AEs (eg, headache, diarrhea, and jaw pain).

A comprehensive description of oral treprostinil, including the pharmacology, toxicology, and clinical studies completed to date can be found in the current Orenitram Investigator's Brochure.

1.3 RATIONALE FOR DEVELOPMENT OF STUDY DRUG IN DISEASE/CONDITION

Orenitram has demonstrated clinical improvements in exercise capacity after 12 weeks of therapy in subjects with WHO Group I pulmonary hypertension (Jing 2013). It is titrated by 0.25 or 0.5 mg BID or 0.125 mg TID every 3 to 4 days, as tolerated (Orenitram United States Prescribing Information [USPI], 2017). Thus, the maximum doses of Orenitram that can be reached are approximately 1 and 3 mg TID at 1 and 3 months, respectively, which in practice is rarely achieved, often because prostanoid side effects limit aggressive dose titration.

Commercial data demonstrate the median TDD of Orenitram at 6 months is 7.5 mg (Balasubramanian 2017). Results from Orenitram clinical studies show that AEs accounted for approximately 50% of all discontinuations of study drug (Jing 2013, Tapson 2012, Tapson 2013). Anecdotal reports from physicians and nurses suggest that AEs leading to drug discontinuation occur early after starting treatment, and that nausea and vomiting are the most common reasons for drug discontinuation.

Results from a recent clinical study suggest PAH patients previously exposed to Remodulin appear to tolerate significantly higher doses of Orenitram as compared to patients without prior Remodulin exposure (Chakinala 2017). The mean TDD of Orenitram achieved in the pivotal clinical studies was approximately 6 mg at 12 to 16 weeks and 8 mg at 1 year, compared with 40 mg at 24 weeks in the Remodulin to Orenitram transition study (Jing 2013, Tapson 2012, Tapson 2013, Orenitram Package Insert, Chakinala 2017).

Aggressive Remodulin titration can be well-tolerated as demonstrated in multiple prospective studies, with doses ranging from 23 to 139 ng/kg/min at 12 weeks (Sitbon 2007, Hansen 2014, Grünig 2016). This is approximately equivalent to Orenitram 4 to 23 mg TID (TDD of 12 to 70 mg) in a 70-kg patient (Orenitram USPI, 2017). In contrast, commercial data suggest the median TDD of Orenitram at 3 months is 4.5 mg (6.38 mg in transition patients and 4.13 mg in de novo patients taking it TID) (Balasubramanian 2017).

In studies that have investigated aggressive Remodulin titration, high doses were often achieved in a short timeframe. In 1 study, patients achieved a mean dose of 52 ng/kg/min by Week 6 (Sitbon 2007). This is approximately equivalent to an Orenitram TDD of 26 mg in a 70-kg patient (Orenitram USPI, 2017). In another study, patients achieved a median dose of 17.2 ng/kg/min by Week 4 (Grünig 2016). This is approximately equivalent to an Orenitram TDD of 8.7 mg in a 70-kg patient (Orenitram USPI, 2017).

Achieving high doses of Orenitram is a goal of many clinicians, as there is evidence suggesting that increased exposure and duration of treatment is associated with improved treatment effect. Post-hoc analysis of FREEDOM-M data suggests that the length of time a patient spends on a TDD greater than 8 mg correlates to a higher combined 6-Minute Walk Distance (6MWD) and Borg dyspnea score effect. In addition, for every 1-mg increase in cumulative daily dose, there is approximately 20% increased odds of achieving a meaningful response to therapy, which was defined as a ≥23-meter change from Baseline in 6MWD (Kumar 2013).

There also appears to be a dose-response relationship for Remodulin. In 1 retrospective review, results suggest that a threshold dose may be associated with improved survival. In this review, the Remodulin dose was a statistically significant on-treatment predictor of survival. Doses ≥40 ng/kg/min resulted in significantly improved long-term survival, and every 10-ng/kg/min incremental dose increase also significantly improved long-term survival (Benza 2011).

1.4 CLINICAL HYPOTHESIS

The hypothesis of this study is that treprostinil induction using a short-term course of Remodulin prior to initiating Orenitram will improve tolerability and allow subjects with PAH to achieve higher daily doses of Orenitram at 16 weeks compared to patients initiating Orenitram de novo.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of the study is to evaluate the dose of Orenitram (treprostinil) Extended Release tablets achieved at 16 weeks after induction therapy with Remodulin (treprostinil) Injection in PAH subjects.

2.2 SECONDARY OBJECTIVES

The secondary objective of the study is to assess the effect of treatment with Orenitram (treprostinil) Extended Release tablets at 16 weeks after induction therapy with Remodulin (treprostinil) Injection on clinical response, safety, and tolerability.

2.3 EXPLORATORY OBJECTIVES

Exploratory objectives of this study are evaluation of pharmacogenomics (genetic/ribonucleic acid [RNA] testing) and evaluation of biomarkers (specific targets to be determined) at Baseline, the Transition Visit, and Week 16.

3 EXPERIMENTAL PLAN

3.1 STUDY DESIGN

The study is a 16-week, open-label, multicenter, uncontrolled study in subjects with PAH.

The following study visits will occur during the 16-week study at the following time points:

- Screening
- Baseline
- Week 2 (Day 15 [±3 days]), Week 4 (Day 29 [±5 days]), Week 8 (Day 57 [±5 days]), Week 12 (Day 85 [±5 days]), and Week 16/Early Study Withdrawal (Day 113 [±7 days])
- Transition Visit may occur at Weeks 2, 4, or 8 if the subject has achieved a minimum Remodulin dose of 20 ng/kg/min and the Investigator deems the subject suitable for transition. Transition may be reversed or stopped if necessary due to significant signs or symptoms of PAH or due to serious safety concerns.
- Post Transition Visit (7 to 14 days after the Transition Visit)

3.2 OVERALL SCHEDULE OF TIMES AND EVENTS

Table 3-1 Overall Schedule of Time and Events

Study Visit/Week	Screening[a]	Baseline[a,b]	Treatment Phase					
			Week 2[s]	Week 4[s,v]	Week 8[s]	Post Transition Visit[v]	Week 12	Week 16/ Early Study Withdrawal[c]
Day	-28 to -1	-14 to -1	15 (±3 days)	29 (±5 days)	57 (±5 days)	7 to 14 days after Transition Visit[v]	85 (±5 days)	113 (±7 days)
Informed consent	X							
Inclusion and exclusion criteria assessment	X	X						
Demographics	X							
PAH history[d]	X							
TSQM[e]		X	----------X[s]----------					X
emPHasis-10 questionnaire[e]		X	----------X[s]----------					X
PAH symptom score		X	----------X[s]----------					X
WHO FC	X	X	X	X	X	X	X	X
Swan-Ganz right heart catheterization[f]	X							
Medical history	X	X						
Prior PAH medications[g]	X	X						
Concomitant medications[g,h]	X	X	X	X	X	X	X	X
Physical examination[i]	X		----------X[s]----------					X
Vital signs[j]	X	X	X	X	X	X	X	X
CD4 count (for subjects with human immunodeficiency virus)	X							

Study Visit/Week	Screening[a]	Baseline[a,b]	Treatment Phase					
			Week 2[s]	Week 4[s,v]	Week 8[s]	Post Transition Visit[v]	Week 12	Week 16/ Early Study Withdrawal[c]
Day	**-28 to -1**	**-14 to -1**	**15 (±3 days)**	**29 (±5 days)**	**57 (±5 days)**	**7 to 14 days after Transition Visit[v]**	**85 (±5 days)**	**113 (±7 days)**
Clinical laboratory parameters (serum chemistry and hematology)	X	X	----------X[s]----------					X
Urine pregnancy test[k]	X	X	X[s]	X	X		X	X
Echocardiogram		X	----------X[s]----------					X
Serum NT-proBNP[l]	X	X	----------X[s]----------					X
Blood sample for pharmacogenomics (genetic/RNA)[m]		X						
Blood sample for biomarker evaluation (optional)[m]		X	----------X[s]----------					X
6MWT followed by heart-rate recovery (1 minute) and Borg dyspnea score[n]	X	X	X[o,p]	X[o,p]	X[o,p]	X[p]	X[p]	X[p]
Study drug dosing[q]		X[r,t]	X[r,t]	X[r,t]	X[r,t]	X[r,t]	X[r,t]	X[r,t]
Recording of adverse events	X	X	X	X	X	X	X	X
AE Bothersome Survey		X	----------X[s]----------					X
Periodic patient contact[u]		X	X	X	X	X	X	
Drug accountability[w]			X	X	X	X	X	X

6MWD, 6-Minute Walk Distance; 6MWT, 6-Minute Walk Test; ECHO, echocardiogram; eCRF, electronic case report form; FC, Functional Classification; IV, intravenous(ly); NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; RHC, right heart catheterization; RNA, ribonucleic acid; SC, subcutaneous(ly); TSQM, Treatment Satisfaction Questionnaire for Medication; WHO, World Health Organization

[a] Screening and Baseline assessments can be conducted up to 28 and 14 days prior to starting the Remodulin infusion, respectively. Screening must occur prior to Baseline assessments to confirm eligibility. Subjects with short-term musculoskeletal conditions (eg, sprained ankle) can be re-screened so that assessments aren't impacted by unusual or extenuating circumstances (refer to Section 7.1.1).

[b] Following completion of Baseline assessments, subjects will be initiated on Remodulin at 2 ng/kg/min SC or IV in an inpatient or outpatient setting. IV Remodulin may be administered through an indwelling central venous catheter or a peripherally inserted catheter, as clinically indicated. For subjects receiving IV Remodulin through a central venous catheter, it is recommended that the central venous catheter be retained for at least 28 days after the transition from Remodulin.

[c] The assessments of Week 16/Early Study Withdrawal Visit can occur over 5 days so that assessments can take place on separate days if needed. All assessments should be conducted prior to withdrawing from the study, prior to discontinuation of Orenitram or Remodulin, and as close as possible to the last dose taken by the subject.

[d] The subject's PAH diagnosis date, past (noncurrent) PAH medications, PAH etiology, and WHO FC will be recorded.

[e] These patient-reported outcomes should be completed by subjects prior to other assessments and before imparting news regarding status of their disease. Subjects should be allowed to complete the questionnaires at their own pace, and with minimal help from others.

[f] Optional: RHC does not need to be conducted if the patient has an RHC within 180 days of Baseline with a cardiac index $\geq$2.0 L/min/m^2 with no changes in PAH medication regimen since the RHC. If an RHC is performed at Screening, values should be obtained for mean right atrial pressure (mRAP) and pulmonary vascular resistance (PVR) to calculate the Screening REVEAL 2.0 risk score.

[g] The subject's prior PAH medications and concomitant medications should be recorded on the eCRF.

[h] The Investigator will record the subject's concomitant medications and record whether the concomitant medication was used to treat an adverse event (including whether prostanoid adverse event or not). For this study, prostanoid adverse events include headache, diarrhea, flushing, nausea, jaw pain, extremity pain, and vomiting.

[i] A full physical examination is an evaluation of general appearance; mental examination; head, ear, eyes, nose, and throat examinations; and examination of dermatologic, cardiovascular, respiratory, gastrointestinal, musculoskeletal, and neurologic body systems.

[j] Vital signs include blood pressure, heart rate, respiration rate, height, and weight. Vital signs must be collected after 5 minutes of rest while seated. No other measurements or procedures should occur during the 5 minutes of rest. Vital signs will be collected prior to or at least 30 minutes after the 6MWT.

[k] Urine pregnancy tests will be conducted on all female subjects of childbearing potential. A negative urine pregnancy test is required of all female subjects of childbearing potential to be eligible for the study and remain enrolled as a subject.

[l] Blood samples for NT-proBNP must be drawn prior to conducting the 6MWT and will occur at the Screening Visit, Baseline Visit (prior to Remodulin initiation), the Transition Visit (prior to Orenitram initiation), and the Week 16/Early Study Withdrawal visit.

[m] Where local regulations allow, the subject's blood sample will be collected for pharmacogenomic (genetic/RNA) and biomarker analysis for those subjects who consent to the optional testing.

[n] The subject should rest (seated) for 10 minutes before each 6MWT. If the 6MWT is conducted using supplemental oxygen at Baseline, then all subsequent 6MWTs during the study should be conducted with supplemental oxygen. Similarly, if the Baseline assessment is conducted without supplemental oxygen, then subsequent assessments should also be conducted without oxygen. All efforts should be made to keep the supplemental oxygen flow rate consistent during the 6MWT. The supplemental oxygen flow rate must be recorded at every 6MWT, if applicable. The Borg dyspnea score and heart rate recovery (1 minute) should take place immediately following the 6MWT.

[o] At the Transition Visit, 6MWT should occur with the subject still on Remodulin therapy, before initiating the transition to Orenitram.

[p] When the subject is receiving Orenitram, the 6MWT should occur within 2 to 6 hours of the subject's most recent dose.

[q] Study drug refers to both Remodulin and Orenitram.

[r] If the Investigator deems a subject unsuitable for transition to Orenitram due to significant signs and symptoms of PAH or any other serious safety concerns, the subject may remain on Remodulin for the duration of the study. The Investigator may reverse, or stop the transition to Orenitram due to concerns of subject safety.

[s] In addition to the scheduled assessments, additional testing will be performed at the Transition Visit as indicated. Subjects may transition at Weeks 2, 4, or 8 if they have achieved a minimum Remodulin dose of 20 ng/kg/min and the Investigator deems the subject suitable for transition. Transition may be reversed or stopped for subject safety.

[t] Subjects should be optimized on Remodulin therapy prior to transition to Orenitram; a dose should be achieved that improves the symptoms of PAH while minimizing excessive pharmacologic effects of Remodulin. Transition from Remodulin to Orenitram will occur over the course of 1 to 21 days.

[u] The study site will contact subjects daily during the first 2 weeks of the study, daily during the transition period (ie, while the subject is on both Remodulin and Orenitram), and twice weekly for the first 2 weeks after transitioning (ie, while the subject is on Orenitram and no longer on Remodulin). At all other time points during the study, subjects will be contacted once weekly.

[v] The Post Transition Visit occurs 7 to 14 days after transition from Remodulin to Orenitram is initiated. If the Transition Visit occurs at Week 2, the Week 4 visit can be substituted for the Post Transition Visit (ie, an extra visit is not necessary).

[w] Study site or pharmacy personnel should assess drug returned and dosing information to confirm drug accountability. See Section 11.5.

3.3 CLINICAL ASSESSMENTS

Subjects will receive drug in an outpatient setting, and clinical laboratory tests will be collected from subjects at the study sites during study visits. Refer to Table 3-1 for the schedules of study assessments. Data will be collected from the Investigator or study site staff entering the subject's data from the study visits into an electronic data capture (EDC) system.

3.3.1 Efficacy

3.3.1.1 Dose of Study Drug

At all study visits that occur while the subject is on study drug, the Investigator will record the dose of Remodulin and/or Orenitram that the patient is taking. For Orenitram, all 3 doses taken in 1 day should be recorded individually (ie, morning, midday, and evening).

3.3.1.2 Pulmonary Arterial Hypertension Symptom Score

The Investigator will assess the subject's PAH symptom score at time points listed in Table 3-1. PAH symptoms include fatigue, dyspnea, lower extremity edema, dizziness, syncope, chest pain, and orthopnea. Symptoms should be scored (grades 0 to 3) as listed in Table 3-2.

Table 3-2 Pulmonary Arterial Hypertension Symptoms

Symptom	Grade			
	0	1	2	3
Fatigue	No fatigue experienced outside of day-to-day living over the past 4 weeks	Average fatigue over the past 4 weeks considered mild	Average fatigue over the past 4 weeks considered moderate	Average fatigue over the past 4 weeks considered severe
Dyspnea	No dyspnea or dyspnea present only with heavy exertion over the past 4 weeks	Average dyspnea over the past 4 weeks considered mild	Average dyspnea over the past 4 weeks considered moderate	Average dyspnea over the past 4 weeks considered severe
Lower extremity edema	No edema experienced over the past 4 weeks	Average edema over the past 4 weeks considered mild	Average edema over the past 4 weeks considered moderate	Average edema over the past 4 weeks considered severe

Symptom	Grade			
	0	1	2	3
Dizziness	No dizziness experienced over the past 4 weeks	Average dizziness over the past 4 weeks considered mild	Average dizziness over the past 4 weeks considered moderate	Average dizziness over the past 4 weeks considered severe
Syncope	No syncope episodes experienced over the past 4 weeks	Infrequent syncope over the past 4 weeks (1 episode)	Somewhat frequent syncope episodes over the past 4 weeks (2 to 3 episodes)	Often over the past 4 weeks (>4 episodes)
Chest pain	No chest pain experienced over the past 4 weeks	Infrequent **and** average severity chest pain over the past 4 weeks considered mild	Somewhat frequent **or** average severity chest pain over the past 4 weeks considered moderate	Often **or** average severity over the past 4 weeks considered severe
Orthopnea	No orthopnea experienced over the past 4 weeks	Average orthopnea over the past 4 weeks considered mild	Average orthopnea over the past 4 weeks considered moderate	Average orthopnea over the past 4 weeks considered severe

3.3.1.3 WHO Functional Classification

WHO Functional Classification (FC) for pulmonary hypertension (Appendix B) will be assessed for subjects at the time points listed in Table 3-1.

3.3.1.4 6-Minute Walk Test

The 6-Minute Walk Test (6MWT) is to evaluate exercise capacity associated with carrying out activities of daily living. All 6MWTs will be conducted by qualified, trained personnel in a designated 6MWT area, which meets the requirements described in Appendix A (American Thoracic Society 2002, Holland 2014). The subject should rest (seated) for at least 10 minutes before every 6MWT. The 6MWT instructions in Appendix A apply to the practice walk, the walks conducted during the time points listed in Table 3-1, and any repeat 6MWT conducted for the study.

3.3.1.4.1 Practice 6-Minute Walk Test

All subjects must have a documented 6MWT conducted at the study site on the course for use during the study. If no previous 6MWT has been conducted at the study site, a practice 6MWT must be conducted at least 1 day prior to the Baseline 6MWT for applicable subjects.

3.3.1.4.2 Baseline 6-Minute Walk Test

The Baseline 6MWT must be conducted prior to initiation of study drug. The Baseline 6MWT must be conducted no sooner than 1 day following the practice 6MWT, for applicable subjects.

The Baseline 6MWT must be conducted free of any unusual or extenuating circumstances (eg, intercurrent illness other than that under study, ankle or knee sprains, unusual pain affecting the lower limbs, respiratory infection, etc). If there is any unusual or extenuating circumstance at Baseline, the visit should be postponed so that there is adequate time for the recovery of the subject. If the 28-day Screening window is exceeded by the subject's recovery, the subject can be re-screened at a later time when the unusual or extenuating circumstance is adequately resolved, so as to not impact the results of the Baseline 6MWT.

NOTE: The Baseline 6MWT (not the practice 6MWT) will be the criterion to assess the subject's eligibility to participate in the study.

3.3.1.4.3 Treatment 6-Minute Walk Tests

6-Minute Walk Tests will be conducted at the time points listed in Table 3-1. At the Transition Visit, the 6MWT should occur with the subject still on Remodulin therapy, before initiating the transition to Orenitram. At the time points after the Transition Visit, the 6MWT should occur within 2 to 6 hours of the subject's most recent dose of Orenitram.

Prior to the start of every 6MWT, the subject should rest (seated) for at least 10 minutes. Borg dyspnea scoring and heart rate recovery (1 minute) should take place immediately following the 6MWT.

If the 6MWT is conducted using supplemental oxygen at Baseline, then all subsequent 6MWTs during the study should be conducted with supplemental oxygen. Similarly, if the Baseline assessment is conducted without supplemental oxygen, then subsequent assessments should also be conducted without oxygen. All efforts should be made to keep the supplemental oxygen flow rate consistent during the 6MWT. Any changes in oxygen therapy

administration between study visits should be noted in the electronic case report form (eCRF). The supplemental oxygen flow rate must be recorded at every 6MWT, if applicable.

In addition, subjects receiving pulmonary rehabilitation prior to study entry should continue on the same schedule up to and including Week 16. Subjects utilizing a walker or cane for stability must also use a walker or cane at every 6MWT during the study.

3.3.1.5 Borg Dyspnea Score

The Borg dyspnea score is a 10-point scale rating the maximum level of dyspnea a subject experiences during the 6MWT (Appendix A). The Borg dyspnea score will be assessed immediately following every 6MWT at time points listed in Table 3-1.

3.3.1.6 Patient-reported Outcomes

The patient-reported outcomes should be completed by the subjects prior to other assessments and before imparting news regarding the status of their disease. Subjects should be allowed to complete the questionnaires at their own pace, and with minimal help from others.

The subject should be informed of the purpose and importance of completing the questionnaires according to the guidelines for standardized administration. The questions should be completed in a quiet place without influence from others. Others should not help a subject answer, interpret, or rephrase the questions for the subject unless absolutely necessary.

Responses to the emPHasis-10© (PHA UK) questionnaire (Appendix H) and the TSQM (Appendix G) for effectiveness, side effects, convenience, and global satisfaction will be collected by study site staff at study visits listed in Table 3-1.

3.3.1.7 Serum N-Terminal Pro-brain Natriuretic Peptide

Serum N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration is a biomarker associated with changes in right heart morphology and function (Fijalkowska 2006). NT-proBNP will be drawn at time points listed in Table 3-1. Samples must be drawn prior to conducting the 6MWT, and will occur at the Screening Visit, the Baseline Visit (prior to Remodulin initiation), the Transition Visit (prior to Orenitram initiation), and the Week 16/

Early Study Withdrawal Visit. Serum NT-proBNP will be assessed by a central clinical laboratory.

3.3.1.8 Echocardiograms

Echocardiogram (ECHO) examinations as assessed by central reader will be conducted at the time points listed in Table 3-1. Echocardiograms will be uploaded and stored in a central repository and evaluated by an independent central reader. Several echocardiographic parameters may be collected, including but not limited to the following: right atrial area, tricuspid annular plane systolic excursion, RV strain, RV/left ventricular ratio at diastole, Eccentricity Index, strain imaging or speckle-tracking; RV Myocardial Performance Index or Tei index; Pulmonary Artery Acceleration Time and presence/timing of Notching; and cardiac output by left ventricular outflow tract diameter and time-velocity integral of aortic flow by pulse-wave Doppler.

All measurements will be made in accordance with the American Society of Echocardiography guidelines. See the ECHO training manual for additional information regarding all methodologies and measures. A central reader will be utilized to assess the echocardiographic data. Echocardiogram images will be stored for central reader access.

3.3.1.9 Demographics, Medical History, PAH History, Concomitant Medications, Prior PAH Medications, Physical Examination

The subject's demographics (birth date, sex, race, and ethnicity), medical history, PAH history (PAH diagnosis date, past [noncurrent] PAH medications, PAH etiology, and WHO FC), and concomitant and prior PAH medications will be recorded as listed in Table 3-1.

The Investigator will record the subject's concomitant medications at time points listed in Table 3-1, and record whether the concomitant medication was used to treat an AE, including whether the AE was a prostanoid AE. For this study, prostanoid AEs include headache, diarrhea, nausea, flushing, jaw pain, extremity pain, and vomiting.

Significant past or present illnesses, current prescription and nonprescription medications (including vitamins, herbal products), and a history of allergies or idiosyncratic responses to drugs should be noted in the eCRF, as required. Any significant changes to the subject's

medical condition, physical examination, and concomitant medications must be documented during the study.

A full physical examination will be conducted at Screening, the Transition Visit, and the Week 16/Early Withdrawal Visit. A full physical examination is an evaluation of general appearance; mental examination; head, ear, eyes, nose, and throat examinations; and examination of dermatologic, cardiovascular, respiratory, gastrointestinal, musculoskeletal, and neurologic body systems.

3.3.2 Safety

3.3.2.1 Adverse Events and the AE Bothersome Survey

Adverse events will be captured from when the subject signs the informed consent form (ICF) until the subject completes the study or is withdrawn from the study. Adverse events should be followed until either resolution (or return to normal or Baseline values), until they are judged by the Investigator to no longer be clinically significant, or for at least 4 weeks if the AE extends beyond the final study visit (Week 16). All serious adverse events (SAEs) that occur during the study will be followed until resolution, death, or the subject is lost to follow-up, even if they are ongoing more than 4 weeks after completion of the final study visit.

The Investigator will administer the AE Bothersome Survey (Appendix E) at time points listed in Table 3-1 to collect information about prostanoid-related effects experienced by the subject. This questionnaire may be used to guide AE assessment and conversations about AEs that a subject is experiencing.

Events related to prostanoid therapy captured by the AE Bothersome Survey (Appendix E) should only be recorded as an AE and should only be captured as an SAE if the event is unusual with respect to intensity, frequency, or duration as compared with symptoms in the subject's medical history.

Events attributable to the progression of the disease under study (listed in Table 9-1) and events attributable to PAH symptomatology captured by PAH Symptom Score (Section

3.3.1.2) should only be recorded as an AE if the event is unusual with respect to intensity, frequency, or duration as compared with symptoms in the subject's medical history, or if there is a reasonable possibility that the event was caused by the study drug

3.3.2.2 Clinical Laboratory Evaluations

A central clinical laboratory will be used to standardize test results. Clinical laboratory assessments will be performed at the time points listed in Table 3-1. For subjects with known human immunodeficiency virus (HIV) infection, CD4 counts may be measured at Screening by either a local laboratory or central laboratory. Clinical laboratory parameters and tests by study visit are displayed in Appendix D.

3.3.2.3 Urine Pregnancy Tests

Urine pregnancy tests will be conducted on all female subjects of childbearing potential. A negative test is required to be eligible for this study and to remain enrolled as a subject.

3.3.2.4 Vital Signs

Vital signs include blood pressure, heart rate, respiration rate, height, and weight. Vital signs should be collected after 5 minutes of rest while seated. No other measurements or procedures should occur during the 5 minutes of rest. Vital signs will be collected prior to or at least 30 minutes after the 6MWT.

3.3.2.5 Periodic Contact with Study Subjects

The study site will contact subjects daily during the first 2 weeks of the study, daily during the transition period (ie, while the subject is on both Remodulin and Orenitram), and twice weekly for the first 2 weeks after transitioning (ie, while the subject is on Orenitram and no longer on Remodulin). At all other time points during the study, subjects will be contacted once weekly.

Subjects may be contacted via email in lieu of a telephone call. Email should not replace direct follow-up by telephone or at the study site for clinically meaningful SAEs or other emergent issues. For telephone calls, the subject contact log should be completed and filed to the subject's source documentation. For emails, a copy of the email must be included in the subject's source documentation.

The telephone calls and/or emails after initiation of study drug and up to Week 16 are to be made between the subject and study site personnel to monitor study drug compliance, AEs, PAH symptoms, use of concomitant medications, and to assess dose titration.

In addition to the periodic contact mentioned above performed by the study site, the Investigator may request that nursing support contact the subject through the duration of Remodulin therapy to monitor study drug compliance, AEs, PAH symptoms, use of concomitant medications, and to assess dose titration.

3.3.3 Other Testing

3.3.3.1 Pharmacogenomic (Genetic/RNA) and Biomarker Testing (Optional)

Where local regulations allow, the subject's blood sample will be collected for pharmacogenomic (genetic/RNA) and biomarker analysis at the time points described in Table 3-1 for those subjects who consent to this optional testing. Genetic blood samples will be stored, and analyses may be performed on genetic variants or gene expression patterns thought to play a role in pulmonary hypertension to evaluate their association with observed response to prostacyclin therapy, including oral treprostinil. Biomarker blood samples will be used for metabolomics with Metabolon, Inc. (Morrisville, NC) and for IP/EP/DP panels.

3.3.3.2 Hemodynamics

Hemodynamics via Swan-Ganz right heart catheterization (RHC) will be assessed during Screening if the subject has not had an RHC within 180 days of Baseline with a cardiac index $\geq$2.0 L/min/m^2 with no changes in their PAH medication regimen (ie, both dosing and drug) since the RHC.

If an RHC is performed at Screening, values should be obtained for mean right atrial pressure (mRAP) and pulmonary vascular resistance (PVR) to calculate the Screening REVEAL 2.0 risk score.

3.4 NUMBER OF CENTERS

Approximately 13 centers in the US will participate in the study.

3.5 NUMBER OF SUBJECTS

Approximately 30 evaluable subjects will be enrolled in this study.

3.6 ESTIMATED STUDY DURATION

The per-subject study period is defined as the date the subject signs the ICF until the Week 16 Visit, the date the subject withdraws from the study, the date a subject dies, or the date a subject is lost to follow-up, whichever occurs first. Subjects who withdraw from study drug prior to Week 16 will be asked to remain in the study up to Week 16 and complete study assessments off treatment.

4 SUBJECT ELIGIBILITY

4.1 INCLUSION CRITERIA

Subjects who meet all the following inclusion criteria will be eligible to participate in the study:

1. Subjects who voluntary give written informed consent to participate in study
2. Males and female subjects aged 18 to 75 years at Screening (date the subject provides written informed consent to participate in study)
3. Subjects with a diagnosis of WHO Group 1 pulmonary hypertension: symptomatic idiopathic or heritable PAH; or PAH associated with connective tissue disease, HIV infection, repaired congenital systemic-to-pulmonary shunt (at least 1 year since repair with respect to the date of providing informed consent), or appetite suppressant/toxin use
4. Subjects with WHO FC II or III symptoms at Baseline
5. Subjects with 6MWD >250 meters at Baseline
6. Subjects who are either not receiving PAH-targeted therapy or are currently being treated with 1 or 2 oral FDA-approved PAH therapies consisting of an endothelin receptor antagonist (ERA) and/or either a phosphodiesterase type-5 inhibitor (PDE5-I) or a soluble guanylate cyclase (sGC) stimulator for ≥45 days, and on a stable dose for ≥30 days prior to the Baseline Visit
7. Subjects should be on stable doses of other medical therapies for at least 10 days prior to the Baseline Visit, with no dose adjustments, additions, or discontinuations. Exceptions to this are discontinuation or dose changes of anticoagulants and/or diuretics. Subjects should not have experienced recent changes to non-pharmacologic interventions, such as exercise, diet plans, pulmonary rehabilitation, sleep apnea treatment, etc for at least 10 days prior to Baseline Visit.
8. Subjects with historical RHC with results consistent with WHO Group 1 PAH, as demonstrated by pulmonary artery pressure mean of ≥25 mmHg, a pulmonary artery

wedge pressure (PAWP) or left ventricular end-diastolic pressure ≤15 mmHg if a PAWP measurement is not available, and a PVR >3 Wood units, in the absence of unrepaired congenital heart disease (other than patent foramen ovale)

9. Subject has undergone an RHC within 180 days of Baseline and had a cardiac index ≥2.0 L/min/m^2 with no changes in their PAH medication regimen (ie, both dosing and drug) since the RHC.
10. Subjects in whom their most recent historical echocardiography demonstrates clinically normal left systolic and diastolic ventricular function and absence of any clinically significant left-sided heart disease. Subjects with clinically insignificant left ventricular diastolic dysfunction due to the effects of RV overload (RV hypertrophy and/or RV dilation) are eligible.
11. Subjects who agree to follow the specified precautions to avoid pregnancy as follows:
    - Subjects who are females of childbearing potential include any female subject who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea for at least 12 consecutive months). For female subjects of childbearing potential, a negative urine pregnancy test is required at Screening and Baseline prior to initiating study drug. Female subjects of childbearing potential must follow 1 of the following approaches:
        - Practice actual abstinence from intercourse
        - Have a partner with a vasectomy
        - Have an intrauterine device
        - Must use 2 different forms of highly effective contraception for the duration of the study, and for at least 48 hours after discontinuing study drug. Medically acceptable forms of effective contraception include approved hormonal contraceptives (such as birth control pills) or barrier methods (such as a condom or diaphragm).
    - Male subjects with a partner of childbearing potential must use a condom during intercourse for the duration of the study, and for 48 hours after discontinuing study drug.
12. Human immunodeficiency virus-positive subjects must have a CD4 lymphocyte count of at least 200 cells/mm^3 within 30 days of Screening and be receiving current standard of care anti-retroviral or other effective medication for the treatment of HIV, with no changes for at least 8 weeks prior to enrollment.
13. Subjects who, in the opinion of the Investigator, are capable of communicating effectively with study personnel and are considered reliable, willing, and likely to be cooperative with protocol requirements and attend all required study visits
14. Subjects who have the capability to answer surveys and questionnaires written in English

4.2 EXCLUSION CRITERIA

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. Female subjects who are pregnant, lactating, or planning to become pregnant during the study
2. Subjects with a current diagnosis of uncontrolled sleep apnea, as defined by their physician
3. Subjects with renal insufficiency, as defined by requiring dialysis or an estimated creatinine clearance of <30 mL/min, as calculated by the Cockcroft-Gault equation (see Appendix F)
4. Subjects with liver dysfunction defined as elevated liver function tests (alanine aminotransferase or aspartate aminotransferase) ≥3 times the upper limit of normal at Screening, or subjects with Child-Pugh Class B or C hepatic disease (see Appendix F)
5. Subjects with anemia, as defined by Screening hemoglobin <9 g/dL
6. Subjects with an active infection or condition that would interfere with interpretation of study assessments
7. Subjects with a history of ischemic heart disease (defined as subjects who require anti-anginal therapy within 6 months of Screening or who have experienced a documented myocardial infarction within 6 months of Screening), or a history of left-sided myocardial dysfunction, as evidenced by a PAWP >15 mmHg or left ventricular ejection fraction <50%
8. Subjects with uncontrolled systemic hypertension, as evidenced by systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg at Baseline
9. Subjects with severe hypotension, as evidenced by systolic blood pressure <90 mmHg or diastolic blood pressure <50 mmHg at Baseline
10. If a lung assessment has been completed as per standard of care, any subject with 1 or more of the following signs of documented relevant lung disease within 180 days of Baseline: total lung capacity <60% of predicted, or forced expiratory volume in 1 second <55% of predicted normal
11. Subjects with chronic musculoskeletal disorder or any other disease that would limit ambulation, or who are connected to a machine that is not portable
12. Subjects with a history of alcohol abuse or illicit drug abuse within 12 months of Baseline which, in the Investigator's opinion, would make the subject inappropriate for enrollment in a clinical study
13. Subjects with any other concomitant disease with life expectancy of <12 months from Baseline
14. Subjects with an unstable psychiatric condition or those not capable of understanding the objectives, nature, or consequences of the study, or who have any condition which, in the Investigator's opinion, would constitute an unacceptable risk to the subject's safety

15. Subjects who are currently receiving an investigational drug, have an investigational device in place, or who have participated in an investigational drug or device study within 180 days prior to Baseline. Participation in an observational study within 180 days prior to Baseline does not disqualify a subject from enrolling.
16. Subjects who have received a prostacyclin-class therapy within 28 days of Baseline.
17. Subjects who have a Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) 2.0 Risk Score of 10 or greater (see Appendix J).

4.3 PRESCRIBED THERAPY

4.3.1 Concomitant Medications

Subjects are eligible for this study if they are either not receiving PAH-targeted therapy or are currently being treated with 1 or 2 FDA-approved oral PAH therapies consisting of an ERA and/or either a PDE5-I or an sGC for ≥45 days. They must be receiving a stable dose for ≥30 days prior to the Baseline Visit. If an FDA-approved treatment for PAH (other than study drug or a prostanoid used in vasoreactivity testing) is added during the study, the subject must be withdrawn from the study.

Subjects should be on stable doses of other medical therapies for at least 10 days prior to Baseline Visit with no dose adjustments, additions, or discontinuations. Exceptions to this are discontinuation or dose changes of anticoagulants and/or diuretics. Medications are also allowed to be temporarily discontinued if necessary for the safety of study-related medical procedures, such as RHC during Screening. Subjects should not have experienced recent changes to non-pharmacologic interventions, such as exercise, diet plans, pulmonary rehabilitation, sleep apnea treatment, etc, for at least 10 days prior to Baseline.

Any concomitant medications taken by the subject during the study should be recorded in the subject's source documents and transcribed to the subject's eCRF.

4.3.2 Other Treatments

During the study, adjustments, additions, or discontinuations of non-pharmacologic interventions, such as exercise, diet plans, pulmonary rehabilitation, sleep apnea treatment, medications approved for PAH, etc, should not occur. Adjustments, additions, or discontinuations of other concomitant medications for other non-PAH diseases can occur.

5 SUBJECT ENROLLMENT

Any subject who meets the inclusion and exclusion criteria will be eligible to enroll in this study. As this is an uncontrolled study, measures to minimize bias and procedures relating to randomization are not applicable.

5.1 TREATMENT ASSIGNMENT

During the study, subjects will be receiving Orenitram and Remodulin supplied by the Sponsor. Subjects who have completed the Week 16 Visit will be transitioned off clinical study material onto commercially available Orenitram or Remodulin, as clinically appropriate.

5.2 RANDOMIZATION

This study does not employ randomization.

5.3 BLINDING

This is an open-label study.

6 DRUGS AND DOSING (OR TREATMENT PROCEDURES)

6.1 DRUG DOSAGE, ADMINISTRATION AND SCHEDULE

Remodulin will be provided in vial strengths of 1 mg/mL, 2.5 mg/mL, 5 mg/mL, and 10 mg/mL. Following completion of Baseline assessments, Remodulin will be initiated at 2 ng/kg/min SC or IV in an inpatient or outpatient setting. IV Remodulin may be administered through an indwelling central venous catheter or a peripherally inserted catheter, as clinically indicated. At the request of the Investigator, nursing support will assist subjects with initiation of SC or IV Remodulin, pump use, Remodulin dispensing, Remodulin titration, and adverse event management. If necessary, subjects can switch from IV to SC Remodulin, or SC to IV Remodulin, at the discretion of the Investigator.

Up-titration of Remodulin will continue as tolerated. Subjects should be optimized on Remodulin therapy prior to transition to Orenitram; a dose should be achieved that improves the symptoms of PAH while minimizing excessive pharmacologic effects of Remodulin. There is no maximum Remodulin dose during the study.

Subjects may transition at Weeks 2, 4, or 8 if they have achieved a minimum Remodulin dose of 20 ng/kg/min and the Investigator deems the subject suitable for transition. Subjects will transition from Remodulin to Orenitram over the course of 1 to 21 days in an inpatient or outpatient setting using a cross-taper method (ie, decreases in Remodulin dose coincide with increases in Orenitram dose). Orenitram will be provided in the extended-release tablet strengths of 0.125 mg, 0.25 mg, 1 mg, 2.5 mg, and 5 mg. Subjects will be instructed to take the appropriate number of 0.125 mg, 0.25 mg, 1 mg, 2.5 mg, and 5 mg tablets based upon their Remodulin dose and the transition schedule chosen by their healthcare provider.

Transition may be reversed or stopped if the Investigator feels it is necessary due to significant signs or symptoms of PAH or due to serious safety concerns. If the Investigator deems a subject unsuitable for transition to Orenitram due to significant signs or symptoms of PAH or any other serious safety concerns, the subject may remain on Remodulin for the duration of the study. However, the subject should be continually assessed to determine if they become stable enough for transition to Orenitram. All subjects still on Remodulin at Week 8 should transition to Orenitram regardless of their Remodulin dose unless the Investigator deems them unsuitable for transition to Orenitram due to significant signs and symptoms of PAH or any other serious safety concerns.

Following completion of transition, Orenitram dose titration will continue in the outpatient setting through Week 16 to reach the maximum tolerated dose by increasing the dose by 0.125 mg TID every 3 to 4 days as tolerated, with the goal of achieving a maximum tolerated dose by the end of Week 16. A slower titration rate may be used if the subject experiences adverse effects. There is no maximum Orenitram dose during the study.

Orenitram will be dosed TID with food. Dosing will take place approximately every 6 to 8 hours, with adjustments permitted based on the subject's lifestyle and schedule. Study subjects should take their study drug at approximately the same times each day. Tablets must be swallowed whole and not chewed, as this will result in inappropriate delivery of the active ingredient. If the tablet is inadvertently damaged during administration, the subject/caregiver should contact site personnel to be monitored for the onset of symptoms due to possible inappropriate drug release. Subjects must not "make-up" or "double-up" on missed doses of

Orenitram. If dosing is interrupted for longer than 24 hours, consideration should be given to gradually re-titrating the subject's dose to the last dose administered prior to the dose interruption, particularly in cases where the last dose prior to interruption was greater than 3 mg.

In the event of a planned short-term treatment interruption for subjects unable to take oral medications after beginning transition to Orenitram, consider a temporary infusion of SC or IV Remodulin using the following equation to calculate the dose of Remodulin:

$$\text{Remodulin (ng/kg/min)} = (139 \times \text{Orenitram TDD [mg]}) \div \text{weight (kg)}$$

Subjects who complete the Week 16 Visit will be transitioned off clinical study material to commercially available Orenitram or Remodulin, as clinically appropriate, through their health and/or prescription insurance. For subjects who are uninsured or underinsured, the study site can help them apply for the United Therapeutics Patient Assistance Program (PAP). Through the PAP, subjects can receive a supply of Orenitram or Remodulin free of charge for a period of 1 year if eligible. After 1 year, subjects may apply for a renewal of PAP assistance on an annual basis. Subjects' eligibility to participate in this program is based on financial inability to pay for the drug, lack of insurance coverage, and other criteria which subjects can discuss with their study site.

6.2 ACCESS TO BLINDED TREATMENT ASSIGNMENT

This study is an open-label study.

6.3 COMPLIANCE

It is anticipated that subjects will follow dosing and titration regimens consistent with the study drug dosing instructions of the study. Routine contact between study site personnel and the subject should be conducted to monitor AEs between scheduled study visits. Study site personnel will record study drug dose at every study visit in the source documentation.

The Investigator, other study site personnel, or nursing support under the direction of the Investigator, will be responsible for dose titration of study drug. During telephone calls, study site personnel and/or nursing support, with oversight of the Investigator, will evaluate and

adjust the current dose of study drug and assess whether the subject is taking the study drug as prescribed.

Arrangements will be made to ensure the subject has adequate drug supply with respect to their study visit schedule. Additional Remodulin and/or Orenitram supply may occur between protocol study visits if needed. Subjects should be instructed to return all used and unused Remodulin and Orenitram, including empty vials/bottles, to the appropriate study personnel on an ongoing basis at every study visit.

Upon return of study drug, study personnel or a pharmacist must document the number of returned tablets of each strength or vials of each strength on the subject's study drug accountability log. Used and unused vials and bottles of study drug should be retained by the study site or pharmacy and returned to a Sponsor-designated location for destruction, or destroyed and documented according to institutional policy following consultation with the Sponsor after final drug accountability by Sponsor personnel.

Every subject will be asked at the study visits whether he/she has been adherent with dosing instructions. If a subject is not adherent, then study site personnel must re-educate the subject on proper dosing and its importance. Continued nonadherence could lead to withdrawal of the subject from the study based on discussions between the Investigator and Sponsor.

7 EXPERIMENTAL PROCEDURES

The following study visits will occur during the 16-week study at the following time points: Screening, Baseline, Week 2 (Day 15 [±3 days]), Week 4 (Day 29 [±5 days]), Week 8 (Day 57 [±5 days]), Post Transition Visit (7 to 14 days after Transition Visit), Week 12 (Day 85 [±5 days]), and Week 16/Early Study Withdrawal (Day 113 [±7 days]). The Transition Visit should occur at Weeks 2, 4, or 8.

Written informed consent must be obtained from all subjects (signed and dated by subject) prior to study procedures. The patient-reported outcomes (ie, TSQM and the emPHasis-10 questionnaire) should be completed by the subjects prior to other assessments listed in Table 3-1. Subject information from assessments listed in Table 3-1, including the

patient-reported outcomes, will be collected and recorded into an EDC system by study site personnel or the Investigator.

7.1 SCREENING (DAYS -28 TO -1)

At Screening, after an Investigator reviews the subject's ICF and obtains the subject's signed and dated written ICF, the Investigator will review and verify the subject's inclusion criteria and exclusion criteria, and assign every eligible subject a unique subject identification. If a subject withdraws from participation in the study, then his/her subject identification cannot be reused. Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled.

All subjects will be assessed for eligibility during the 28-day Screening window. The following Investigator-reported assessments will be conducted after the subject signs the ICF:

- WHO FC assessment
- Serum NT-proBNP (sample must be drawn prior to the 6MWT initiation)
- 6MWT (after 10 minutes rest [seated]), immediately followed by heart rate recovery (1 minute) and Borg dyspnea score
- Clinical laboratory assessments
- Vital signs (prior to or at least 30 minutes after the 6MWT, and after 5 minutes of rest seated)
- Full physical examination
- Concomitant medications
- CD4 count for subjects with HIV infection
- Female subjects of childbearing potential will undergo a urine pregnancy test.
- Subject AEs will be recorded continuously from when the subject signs the ICF until the subject completes the study or is withdrawn from the study.
- The subject's medical history, PAH history, prior PAH medications, and demographics will be recorded.
- Cardiac index measured by Swan-Ganz RHC will be assessed during Screening if the subject has not had an RHC within 180 days of Baseline with a cardiac index $\geq$2.0 L/min/m^2 with no changes in PAH medication regimen since the RHC

7.1.1 Re-screening of Subjects

Subjects with short-term musculoskeletal conditions (eg, sprained ankle) can be re-screened. The Baseline 6MWT must be conducted free of any unusual or extenuating circumstances (eg, intercurrent illness other than that under study, ankle or knee sprains, unusual pain affecting the lower limbs, respiratory infection, etc). If there is any unusual or extenuating circumstance at Baseline, the visit should be postponed so that there is adequate time for the recovery of the subject. If the 28-day Screening window is exceeded by the subject's recovery, the subject can be re-screened at a later time when the unusual or extenuating circumstance is adequately resolved, so as to not impact the results of the Baseline 6MWT.

7.2 BASELINE (DAYS -14 TO -1)

The following subject-reported data will be completed by the subject at Baseline prior to all other assessments: emPHasis-10 questionnaire and TSQM.

Baseline assessments can be conducted up to 14 days prior to starting the Remodulin infusion. The following Investigator-reported assessments will be conducted:

- Inclusion and exclusion criteria assessment
- ECHO
- WHO FC assessment
- Serum NT-proBNP (sample must be drawn prior to the 6MWT and Remodulin initiation)
- 6MWT (after 10 minutes rest [seated]), immediately followed by heart rate recovery (1 minute) and Borg dyspnea score
- Clinical laboratory assessments
- Vital signs (prior to or at least 30 minutes after the 6MWT, and after 5 minutes of rest seated)
- Concomitant medications
- Optional pharmacogenomic (genetic/RNA) and biomarker blood samples
- Female subjects of childbearing potential will undergo a urine pregnancy test
- Subject AEs will be recorded
- AE Bothersome Survey
- The subject's medical history, PAH symptom score, and prior PAH medications will be recorded.

7.3 TREATMENT PHASE

Following completion of Baseline assessments, Remodulin will be initiated at 2 ng/kg/min SC or IV in an inpatient or outpatient setting. Intravenous Remodulin may be administered through an indwelling central venous catheter or a peripherally inserted catheter as clinically indicated. For subjects receiving IV Remodulin through a central venous catheter, it is recommended that the central venous catheter be retained for at least 28 days after the transition from Remodulin.

Up-titration of Remodulin will continue as tolerated. Subjects should be optimized on Remodulin therapy prior to transition to Orenitram; a dose should be achieved that improves the symptoms of PAH while minimizing excessive pharmacologic effects of Remodulin. There is no maximum Remodulin dose during the study. If necessary, subjects can switch from IV to SC Remodulin, or SC to IV Remodulin, at the discretion of the Investigator.

Periodic contact between study site personnel and subjects should be conducted to monitor AEs between scheduled study visits (see Section 3.3.2.5). At the request of the Investigator, nursing support will assist subjects with initiation of SC or IV Remodulin, pump use, Remodulin dispensing, Remodulin titration, adverse event management, and transition assistance. Once the subject fully transitions off Remodulin, the study site will be the subject's primary/sole contact. Study site personnel will record the study drug dose at every study visit in the source documentation.

7.3.1 Week 2 (Day 15 [±3 Days])

Subjects will continue study drug dosing in the outpatient setting, as clinically appropriate. Subjects will return to the study site clinic for the following Investigator-reported assessments:

- Record of AEs
- WHO FC
- 6MWT (after 10 minutes rest [seated]), immediately followed by heart rate recovery (1 minute) and Borg dyspnea score. If the subject is receiving Orenitram, the 6MWT should occur within 2 to 6 hours of the most recent dose.
- Concomitant medications

- Vital signs (prior to or at least 30 minutes after the 6MWT, and after 5 minutes rest seated)
- Drug accountability (see Section 11.5)
- If the Transition Visit occurs at Week 2, please perform additional assessments listed in Section 7.3.4.

7.3.2 Week 4 (Day 29 [±5 Days])

Subjects will continue study drug dosing in the outpatient setting, as clinically appropriate.

Subjects will return to the study site clinic for the following Investigator-reported assessments:

- Record of AEs
- WHO FC
- 6MWT (after 10 minutes rest [seated]), immediately followed by heart rate recovery (1 minute) and Borg dyspnea score. If the subject is receiving Orenitram, the 6MWT should occur within 2 to 6 hours of the most recent dose.
- Concomitant medications
- Vital signs (prior to or at least 30 minutes after the 6MWT, and after 5 minutes rest seated)
- Female subjects of childbearing potential will undergo a urine pregnancy test
- Drug accountability (see Section 11.5)
- If the Transition Visit occurs at Week 4, please perform additional assessments listed in Section 7.3.4.

Note: If the Transition Visit occurs at Week 2, the Week 4 visit can be substituted for the Post Transition Visit (ie, an extra visit is not necessary).

7.3.3 Week 8 (Day 57 [±5 Days])

Subjects will continue study drug dosing in the outpatient setting, as clinically appropriate.

Subjects will return to the study site clinic for the following Investigator-reported assessments:

- Record of AEs
- WHO FC
- 6MWT (after 10 minutes rest [seated]), immediately followed by heart rate recovery (1 minute) and Borg dyspnea score. If the subject is receiving Orenitram, the 6MWT should occur within 2 to 6 hours of the most recent dose.

- Concomitant medications
- Vital signs (prior to or at least 30 minutes after the 6MWT, and after 5 minutes rest seated)
- Female subjects of childbearing potential will undergo a urine pregnancy test
- Drug accountability (see Section 11.5)
- If the Transition Visit occurs at Week 8, please perform additional assessments listed in Section 7.3.4.

7.3.4 Transition Visit (Week 2, 4, or 8)

Subjects may transition at Weeks 2, 4, or 8 if they have achieved a minimum Remodulin dose of 20 ng/kg/min and the Investigator deems the subject suitable for transition. Subjects will transition from Remodulin to Orenitram over the course of 1 to 21 days in an inpatient or outpatient setting using a cross-taper method (ie, decreases in Remodulin dose coincide with increases in Orenitram dose). Subjects will be instructed to take the appropriate number of Orenitram tablets based upon their Remodulin dose and the transition schedule chosen by their healthcare provider.

At the discretion of the Investigator, transition may also be reversed or stopped if necessary due to significant signs or symptoms of PAH or due to serious safety concerns. If the Investigator deems a subject unsuitable for transition to Orenitram due to significant signs and symptoms of PAH or any other serious safety concerns, the subject may remain on Remodulin for the duration of the study. However, the subject should be continually assessed to determine if they become stable enough for transition to Orenitram. All subjects still on Remodulin at Week 8 should transition to Orenitram at Week 8 regardless of their Remodulin dose unless the Investigator deems them unsuitable for transition to Orenitram due to significant signs and symptoms of PAH or any other serious safety concerns.

Transition will occur as follows:

- The dose of Remodulin can be reduced no more than 10 ng/kg/min per day for transitions in the outpatient setting. For inpatient transitions, there is no limit on the rate of Remodulin dose reduction.
- The target dose of Orenitram at the end of transition is dependent on the subject's weight and Remodulin dose. Up-titration of Orenitram should coincide with a reduction in the Remodulin dose. The target TDD of Orenitram at the end of

transition will be calculated based upon the following equivalence weight-based formula:

TDD [mg] = 0.0072 * Remodulin dose [ng/kg/min] * weight [kg].

- The Orenitram up-titration dose should be taken at approximately the same time the Remodulin dose is decreased.
- Examples of transition schedules for various subject body weights and Remodulin doses are listed in Appendix I.

The following subject-reported data will be completed by the subject at the Transition Visit prior to all other assessments and prior to initiation of Orenitram: emPHasis-10 questionnaire and TSQM.

The following assessments should be performed at the Transition Visit:

- PAH symptom score
- Record of AEs
- AE Bothersome Survey
- WHO FC
- Serum NT-proBNP (sample must be drawn prior to the 6MWT and Orenitram initiation)
- 6MWT (after 10 minutes rest [seated]), immediately followed by heart rate recovery (1 minute) and Borg dyspnea score (before initiating the transition to Orenitram)
- Concomitant medications
- Full physical examination
- ECHO
- Vital signs (prior to or at least 30 minutes after the 6MWT, and after 5 minutes rest seated)
- Female subjects of childbearing potential will undergo a urine pregnancy test
- Drug accountability (see Section 11.5)
- Clinical laboratory assessments
- Optional biomarker blood sample

Following transition, Orenitram dose titration may continue in the outpatient setting through Week 16 to reach the maximum tolerated dose by increasing the dose by 0.125 mg TID every 3 to 4 days as tolerated, with the goal of achieving a maximum tolerated dose by the end of

Week 16. A slower titration rate may be used if the subject experiences adverse effects. There is no maximum Orenitram dose during the study.

7.3.5 Post Transition Visit (7 to 14 days after Transition Visit)

Subjects will continue study drug dosing in the outpatient setting, as clinically appropriate. Subjects will return to the study site clinic for the following Investigator-reported assessments:

- Record of AEs
- WHO FC
- 6MWT (after 10 minutes rest [seated]), immediately followed by heart rate recovery (1 minute) and Borg dyspnea score. The 6MWT should occur within 2 to 6 hours of the most recent dose of Orenitram.
- Concomitant medications
- Vital signs (prior to or at least 30 minutes after the 6MWT, and after 5 minutes rest seated)
- Drug accountability (see Section 11.5)

Note: If the Transition Visit occurs at Week 2, the Week 4 visit can be substituted for the Post Transition Visit (ie, an extra visit is not necessary).

7.3.6 Week 12 (Day 85 [±5 Days])

Subjects will continue study drug dosing in the outpatient setting, as clinically appropriate. Subjects will return to the study site clinic for the following Investigator-reported assessments:

- Record of AEs
- WHO FC
- 6MWT (after 10 minutes rest [seated]), immediately followed by heart rate recovery (1 minute) and Borg dyspnea score. If the subject is receiving Orenitram, the 6MWT should occur within 2 to 6 hours of the most recent dose.
- Concomitant medications
- Vital signs (prior to or at least 30 minutes after the 6MWT, and after 5 minutes rest seated)
- Female subjects of childbearing potential will undergo a urine pregnancy test
- Drug accountability (see Section 11.5)

7.3.7 Week 16/Early Study Withdrawal (Day 113 [±7 Days])

The following subject-reported data will be completed by the subject at the Week 16/Early Study Withdrawal Visit prior to all other assessments: emPHasis-10 questionnaire and TSQM.

The assessments of Week 16/Early Study Withdrawal Visit can occur over 5 days so that assessments can take place on separate days if needed. All assessments should be conducted prior to withdrawing from the study, prior to discontinuation of Orenitram or Remodulin, and as close as possible to the last dose taken by the subject.

Subjects will return to the study site clinic for the following Investigator-reported assessments:

- PAH symptom score
- Record of AEs
- AE Bothersome Survey
- ECHO
- WHO FC
- Serum NT-proBNP (samples must be drawn prior to the 6MWT)
- 6MWT (after 10 minutes rest [seated]), immediately followed by heart rate recovery (1 minute) and Borg dyspnea score. If the subject is receiving Orenitram, the 6MWT should occur within 2 to 6 hours of the most recent dose.
- Clinical laboratory assessments
- Vital signs (prior to or at least 30 minutes after the 6MWT, and after 5 minutes rest seated)
- Concomitant medications
- Full physical examination
- Optional biomarker blood sample
- Female subjects of childbearing potential will undergo a urine pregnancy test
- Drug accountability (see Section 11.5)

Subjects who complete the Week 16 Visit will be transitioned off clinical study material to commercially available Orenitram or Remodulin, as clinically appropriate.

8 STUDY TERMINATION

8.1 CRITERIA FOR SUBJECT WITHDRAWAL

A subject may voluntarily withdraw or be withdrawn from the study and/or study drug by the Investigator at any time for reasons including, but not limited to, the following:

- The subject wishes to withdraw from further participation.
- A serious or life-threatening AE occurs or the Investigator considers that it is necessary to discontinue study drug to protect the safety of the subject.
- The subject deviated from the protocol.
- The subject's behavior is likely to undermine the validity of his/her results.

If a subject is discontinued from the study prematurely, the Investigator must provide an explanation in the eCRF (Investigator's Comment Log) and complete the End of Study Record for that subject. If study drug has been administered, the Investigator should make every effort to perform all scheduled evaluations prior to discharge. In the event that a subject discontinues study drug prematurely due to an AE, the subject will be followed until either the Investigator determines that the AE has resolved, it is no longer considered clinically significant, the subject is lost to further follow-up, or for 4 weeks if the AE extends beyond the final visit.

If a subject discontinues study drug prior to completing the Week 16 Visit assessments, the Investigator will record the reason for withdrawal (eg, type of AE, lack of response), the dosing titration schedule (date and dose of last titration, date and last dose taken before study drug discontinuation), and if transitioning to a different pulmonary hypertension therapy, the pulmonary hypertension drug to which the subject is transitioning.

8.2 CRITERIA FOR TERMINATING THE STUDY

The study may be stopped at any time if, in the opinion of the Investigator and/or Sponsor, continuation of the study represents a serious medical risk to the subjects. This may include, but is not limited to, the presence of serious, life-threatening, or fatal AEs or AEs that are unacceptable in nature, severity, or frequency. The Sponsor reserves the right to discontinue the study for any reason at any time.

8.3 CRITERIA FOR DISCONTINUING THE SITE

The study may also be terminated at a given center if:

- The Investigator elects to discontinue the study
- The Sponsor elects to discontinue the study at the study site
- United States FDA regulations or International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines are not observed
- The protocol is violated or critical violations are documented, or
- Changes in personnel or facilities adversely affect performance of the study

9 ADVERSE EVENT REPORTING

9.1 DEFINITIONS

9.1.1 Adverse Event

An AE is any untoward medical occurrence in a subject occurring to a subject during a clinical study whether or not it is related to the study drug. An AE may include an intercurrent illness, injury, or any other concomitant impairment of the subject's health, as well as abnormal laboratory findings if deemed to have clinical significance. Adverse events may also include worsening of an existing symptom or condition or post-treatment events that occur as a result of protocol-mandated procedures.

Events related to prostanoid therapy captured by the AE Bothersome Survey (Appendix E) should only be recorded as an AE and should only be captured as an SAE if the event is unusual with respect to intensity, frequency, or duration as compared with symptoms in the subject's medical history.

Events attributable to the progression of the disease under study (listed in Table 9-1) and events attributable to PAH symptomatology captured by PAH Symptom Score (Section 3.3.1.2) should be recorded as an AE or captured as an SAE if the event is unusual with respect to intensity, frequency, or duration as compared with symptoms in the subject's medical history, or if there is a reasonable possibility that the event was caused by the study drug.

Table 9-1 Adverse Events Attributable to the Progression of Disease

Anorexia	Palpitations
Abdominal pain	Peripheral edema/generalized edema
Dizziness	Presyncope
Dyspnea/dyspnea on exertion	Pulmonary hypertension, exacerbation of
Exercise tolerance decreased	Right heart failure/right ventricular failure
Fatigue	Syncope
Hypoxia	Weight loss
Lethargy	Weight gain
Loss of consciousness	

Note: Symptoms of right ventricular failure/right heart failure can include, but are not limited to, ascites, cyanosis, tachycardia, and other cardiac arrhythmias. The effects of pulmonary hypertpension and right ventricular failure/right heart failure can include cardiac arrest and death.

9.1.2 Serious Adverse Event

An SAE is an AE occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Results in a medically important event or reaction

In addition, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and require medical/surgical intervention to prevent 1 of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Life-threatening means that the subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred. It does not mean that the event, had it occurred in a more severe form, might have caused death.

For this study, SAE reporting responsibilities will be as per Section 9.3. All SAEs that occur during the study will be followed until resolution, death, or the subject is lost to follow-up, even if they are ongoing more than 30 days after completion of the final study visit (Week 16 Visit or Early Withdrawal Visit).

9.2 DOCUMENTATION OF ADVERSE EVENTS

An AE or SAE occurring during the study must be documented in the subject's source documents and on the appropriate eCRF page. Information relating to the AE, such as onset and cessation dates and times, intensity, seriousness, relationship to the study drug, and outcome, is to be documented in the eCRF (see Appendix C). If several signs or symptoms are clearly related to a medically defined diagnosis or syndrome, the diagnosis or syndrome should be recorded on the eCRF page, not the individual signs and symptoms.

All AEs should be followed until either resolution (or return to normal or Baseline values), until they are judged by the Investigator to no longer be clinically significant, or for at least 4 weeks if the AE extends beyond the final visit. All SAEs that occur during the study will be followed until resolution, death, or the subject is lot to follow-up, even if they are ongoing more than 4 weeks after completion of the final visit. Supplemental measurements and/or evaluations may be necessary to investigate fully the nature and/or causality of an AE or SAE. This may include additional laboratory tests, diagnostic procedures, or consultation with other healthcare professionals. The eCRF pages should be updated with new or additional information.

The AEs reported by the subjects will be summarized by United Therapeutics Corporation during the study at intervals aligned with periodic safety update reports and at the end of the study.

For any nonserious AE that is outside the scope of the prostanoid AEs (headache, diarrhea, nausea, flushing, jaw pain, extremity pain, and vomiting) that subjects will be reporting during this study, the Investigator will be instructed to report the AEs in compliance with the FDA reporting responsibilities (MedWatch/spontaneous).

9.3 REPORTING RESPONSIBILITIES OF THE INVESTIGATOR

All SAEs, regardless of expectedness or causality, must be reported in the ClinTrak EDC system within 24 hours of awareness. Follow-up SAE information should be reported to United Therapeutics GDS within 24 hours of the receipt of any new/updated information by entering it into the EDC system.

In the event the ClinTrak EDC system is unavailable, the SAE should be reported on the SAE Notification Form to United Therapeutics GDS by e-mail or fax [redacted]; Fax-Americas/Japan [redacted]) in order to meet the 24-hour reporting deadline. The SAE must be recorded in the ClinTrak EDC system as soon as it becomes available. Any relevant medical records should be sent to United Therapeutics GDS by fax or email.

Serious AEs (which the study site was unaware of) that are reported directly to United Therapeutics GDS by the contract research organization or nursing support will be forwarded to the study site. Study site personnel shall record these events in the EDC.

The Investigator must also promptly notify their Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of the SAE, including any follow-up information, in accordance with applicable national regulations and guidelines set forth by the IRB/IEC.

9.4 SAFETY REPORTS

In accordance with FDA, European, and national regulations, the Sponsor will notify the FDA, other competent authorities, and all participating Investigators of any AE that is considered possibly attributable to study drug and is both serious and unexpected. The Investigator must report these AEs to their IRB or ethics committee in accordance with applicable national regulations and guidelines set forth by the IRB or ethics committee.

9.5 PREGNANCY

If a subject becomes pregnant during participation in the clinical study, study site staff must notify the Sponsor within 24 hours of learning of the pregnancy by completing the Pregnancy Notification and Outcome Form and submitting via fax or e-mail to United Therapeutics GDS by e-mail or fax [redacted]; fax: [redacted]). United Therapeutics GDS will follow-up with the Investigator to ensure appropriate data are listed regarding the

outcome of the pregnancy. If the outcome of the subject's pregnancy meets the criteria for immediate classification of an SAE (including, but not limited to, stillbirth, spontaneous abortion, postpartum complication, neonatal death, or congenital anomaly), the Investigator in the study should follow the steps for reporting an SAE. Subjects who become pregnant during the study will be withdrawn from active participation in the study and will discontinue study drug.

10 STATISTICAL CONSIDERATIONS

10.1 DATA PROCESSING

The study will collect data obtained from participating subjects in the ClinTrak EDC system.

10.1.1 EDC

Data will be recorded on the eCRF, and eCRFs will be completed for each subject. Limited data will be recorded on screen failures. Data will be transcribed into an eCRF by the appropriate study site personnel for each subject until study completion, or study discontinuation for any reason. The Sponsor or designee will verify eCRF data fields against source documentation. All data entered in the eCRF by the study site will be entered into a quality assured computerized database. Any discrepancies will be posted in the system for resolution by the site. The eCRF data for every subject is to be reviewed by the Investigator for completeness and accuracy. The Investigator must electronically sign every subject's eCRF to signify their approval of the data. The Investigator will be required to re-sign an eCRF if changes are made to a subject's eCRF by the study site after the Investigator has applied his/her signature. The database will be considered final when all outstanding queries have been resolved and all data management quality assurance procedures are complete.

10.2 SAMPLE SIZE

A sample size of approximately 30 evaluable subjects was set for feasibility and to ensure a reasonable dataset to evaluate the Orenitram dose achieved, the clinical response with an induction period with Remodulin, and to assess the safety and tolerability of Orenitram after induction therapy with Remodulin. No formal sample size computation was performed with respect to the primary endpoint.

10.3 ANALYSIS PLAN

No formal hypothesis is being tested. The efficacy and safety data in the study will be presented in summary tables and listings in the final clinical study report. Listings will be sorted by subject, visit, and time point assessment (if applicable). For summary tables, the data will be summarized by visits and time point assessment, if appropriate. For continuous variables, descriptive statistics will include the number of observations, mean, SD, median, minimum, and maximum. For categorical variables, descriptive statistics will include the frequency and percentage in every category. Details of efficacy and safety analyses are provided below. Further details will be documented in a statistical analysis plan.

The Safety Population is defined as all subjects in the study who receive study drug (Remodulin or Orenitram). All safety and efficacy analyses will be performed on the Safety Population.

10.3.1 Primary Endpoint

10.3.1.1 Efficacy Endpoint

The primary efficacy endpoint of the percentage of subjects achieving an Orenitram dose of 4 mg TID (or a total daily dose of 12 mg) or higher at Week 16 (or a dose of 0.057 mg/kg TID [or a total daily dose of 0.171 mg/kg] or greater for subjects <70 kg) will be calculated and summarized.

10.3.2 Secondary Endpoints

10.3.2.1 Safety Endpoints

10.3.2.1.1 Prostanoid Adverse Events

Prostanoid AE scores captured by the Prostacyclin Bothersome Score will be summarized at Baseline, the Transition Visit, and Week 16/Early Study Withdrawal.

10.3.2.2 Efficacy Endpoints

The following secondary efficacy endpoints will be summarized:

- Change in 6MWD from Baseline to the Transition Visit and Week 16
- Change in Borg dyspnea score from Baseline to the Transition Visit and Week 16
- Change in WHO FC from Baseline to the Transition Visit and Week 16

- Change in NT-proBNP levels from Baseline to the Transition Visit and Week 16
- Echocardiographic parameters will be summarized at Baseline, the Transition Visit, and Week 16.
- PAH symptom score at Baseline, the Transition Visit, and Week 16
- Health-related quality of life (emPHasis-10) at Baseline, the Transition Visit, and Week 16
- The percentage of subjects that improve in each of the following 4 individual clinical parameters at Week 16 (6MWD, NT-proBNP, WHO FC, right atrial area) to a lower risk stratum, as defined by the 2015 European Society of Cardiology guidelines, compared to Baseline
- The percentage of subjects that meet each of the following 4 individual clinical parameters at Week 16 in the low risk category, as defined by the 2015 European Society of Cardiology guidelines: 6MWD >440 meters, serum NT-proBNP <300 ng/L, WHO FC I or II, and right atrial area <18 cm^2
- The percentage of subjects that either achieve an Orenitram dose of 4 mg TID (or a total daily dose of 12 mg) or higher at Week 16 (or a dose of 0.057 mg/kg TID [or a total daily dose of 0.171 mg/kg] or greater for subjects <70 kg) or the percentage of subjects that achieve an Orenitram dose ≥2 mg TID and <4 mg TID (or a total daily dose ≥6 mg and <12 mg) at Week 16, with at least 2 of the following 3 clinical parameters at Week 16 calculated and summarized: 6MWD increase by ≥10% or ≥30 meters from Baseline, serum NT-proBNP reduction >30% from Baseline, or WHO FC I or II
- The percentage of subjects that successfully transitioned to Orenitram at any dose and were successfully maintained on therapy at Week 16

10.3.2.2.1 Patient-reported Outcomes

Subjects' TSQM responses and emPHasis-10 questionnaires will be summarized at Baseline, Transition Visit, and Week 16/Early Study Withdrawal.

10.3.3 Safety Analyses

The Safety Population will be defined as all subjects in the study that receive study drug. All safety analyses will be performed on the Safety Population. Safety will be evaluated by assessment of AEs, clinical laboratory evaluations, and vital signs. All AEs as recorded by the Investigators will be assigned Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms by the Sponsor for reporting purposes. For all safety endpoints, tabular summaries will be provided.

10.4 INTERIM ANALYSIS

No interim analysis during the study is planned.

10.5 OTHER ANALYSES

Other exploratory, post-hoc analyses may be conducted based on available study data.

10.6 DATA LISTINGS AND SUMMARIES

All data gathered in this study will be presented in summary tables and listings in the final clinical study report. In general, listings will be sorted by subject and scheduled assessment (if applicable). For summary tables, data will be summarized by scheduled assessment. For continuous variables, descriptive statistics will include the number of observations, mean, SD, median, inter-quartile range, minimum, and maximum. For categorical variables, descriptive statistics will include the frequency and percent in each category.

11 PACKAGING AND FORMULATION

11.1 CONTENTS OF STUDY DRUG

United Therapeutics Corporation will supply study drug for administration during the study.

The oral treprostinil tablets are SR osmotic tablets. Active treatment will be oral treprostinil tablets provided as 0.125-, 0.25-, 1-, 2.5-, and 5-mg strengths for the study. Each tablet contains either 0.125 mg treprostinil (equivalent to 0.159 mg treprostinil diolamine), 0.25 mg treprostinil (equivalent to 0.317 mg treprostinil diolamine), 1 mg treprostinil (equivalent to 1.27 mg treprostinil diolamine), 2.5 mg treprostinil (equivalent to 3.17 mg treprostinil diolamine), or 5 mg treprostinil (equivalent to 6.34 treprostinil diolamine). The 0.125-, 0.25-, 1-, 2.5-, and 5-mg tablets are colored white, green, yellow, pink, and red, respectively. Oral treprostinil tablets will be provided in child resistant bottles, each containing 100 tablets.

Parenteral treprostinil is supplied as a sterile solution formulated for SC or IV administration. Remodulin is supplied in 20-mL multidose vials in 4 strengths, containing 20 mg, 50 mg, 100 mg, or 200 mg (1 mg/mL, 2.5 mg/mL, 5 mg/mL, or 10 mg/mL, respectively) of treprostinil. Each milliliter also contains 5.3 mg sodium chloride (except for the 10 mg/mL strength, which contains 4.0 mg sodium chloride), 3 mg metacresol, 6.3 mg sodium citrate,

and water for injection. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2.

Subjects who have completed the Week 16 Visit will be transitioned off clinical study material to commercially available Orenitram or Remodulin, as clinically appropriate.

11.2 LABELING

Commercial drug supply is being used in this study. Every bottle of Orenitram and each package of Remodulin is labeled in accordance with applicable national regulations, to include at least the following information: study drug name; strength; quantity; route of administration; manufacture or expiry date; lot number; Sponsor name, address, and telephone number; and storage conditions.

In addition, Remodulin and Orenitram provided to subjects will have an additional clinical study label which will bear the following: the study reference code, a unique serialized package number, and the following message – "CAUTION: NEW DRUG—LIMITED BY FEDERAL LAW TO INVESTIGATIONAL USE."

11.3 STORAGE AND HANDLING OF CLINICAL STUDY MATERIAL

Study drug at the study site will be stored in a securely locked cabinet or enclosure with appropriate temperature monitoring. Access should be strictly limited to the Investigators and their designees. All study drug will be stored at a controlled temperature of 25°C (77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F).

Remodulin study drug vials must be used or discarded within 30 days of initial puncture. Remodulin solution can be administered SC for up to 72 hours at 37°C or IV for up to 48 hours at 40°C. Broken or damaged Orenitram tablets should not be ingested but should be returned to the study site.

11.4 SUPPLY AND RETURN OF CLINICAL STUDY MATERIAL

Arrangements will be made to ensure the subject has adequate drug supply with respect to their study visit schedule. Additional Remodulin and/or Orenitram supply may occur between protocol study visits if needed. Subjects should be instructed to return all used and unused

Remodulin and Orenitram, including empty vials/bottles, to the appropriate study personnel on an ongoing basis at every study visit.

Used and unused vials and bottles of study drug should be retained by the study site and returned to a Sponsor-designated location for destruction, or destroyed and documented according to institutional policy following consultation with the Sponsor after final drug accountability by Sponsor personnel or delegate.

11.5 DRUG ACCOUNTABILITY

The Investigator is responsible for study drug accountability and reconciliation overall and on a per subject basis. Drug accountability records will be maintained during the study, and these records will include the amount of study drug received from the Sponsor, the amount dispensed to each subject, and the amount of unused drug or empty containers. Study site or pharmacy personnel should assess drug returned and dosing information to confirm drug accountability. Once a representative from the Sponsor is able to confirm drug accountability for that subject, study drug can be returned to a Sponsor-designated location for destruction, or destroyed and documented according to institutional policy following consultation with the Sponsor after final drug accountability by Sponsor personnel or delegate.

12 REGULATORY AND ETHICAL OBLIGATION

12.1 US FDA OR APPLICABLE REGULATORY REQUIREMENTS

The study will be conducted in accordance with ICH and GCP guidelines and all applicable national regulations. The Sponsor will obtain the required approval from each national regulatory authority to conduct the study. During the conduct of the study, an annual safety report will be compiled by the Sponsor for submission to those regulatory authorities and IRBs/ethics committees that require it. Any additional national reporting requirements as specified by the applicable regulations, regulatory authorities, or IRB/ethics committee will also be fulfilled during the conduct of the study.

12.2 INFORMED CONSENT REQUIREMENTS

Before a subject is enrolled in the study, the Investigator or his/her designees must explain the purpose and nature of the study, including potential benefits and risks and all study procedures to the subject. The subject must sign and date an IRB/ethics committee-approved ICF prior to the conduct of any study-related activities. A copy of the signed consent form will be given to the subject, and the original will be retained in the study site's records.

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB/IEC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB/IEC, and/or regulatory agencies.

12.3 INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD

Prior to study initiation at each site, the Investigator will obtain approval for the study from an appropriate IRB/IEC and provide the Sponsor with a copy of the approval letter. The IRB/IEC must also review and approve the study site's ICF, protocol, Investigator's Brochure, safety updates, annual progress reports, and any other written information provided to the subject prior to enrollment, as well as any advertising materials used for subject recruitment. Copies of the ICF and advertising materials must be forwarded to the Sponsor for review before submission to the IRB/IEC prior to the start of the study.

If, during the study, it is necessary to amend either the protocol or the ICF, the Investigator is responsible for obtaining IRB/IEC approval of the amended documents prior to implementation. Copies of the IRB/IEC correspondence and approval letters must be sent to the Sponsor.

During the conduct of the study, an annual progress report will be compiled by the Sponsor for submission to those IRBs/IECs that require it.

A written summary of the study will be supplied by the Investigator to the IRB/IEC following study completion or termination according to the IRB's or IEC's standard procedures. Additional updates will be supplied in accordance with the IRB/IEC's standard procedures.

12.4 PRESTUDY DOCUMENTATION REQUIREMENTS

Prior to the commencement of the clinical study, the following documents will be provided to the site: Investigator's Brochure, approved Orenitram USPI, approved Remodulin USPI, protocol, ICF, budget agreement, and eCRF Completion Guidelines.

The study site will be required to provide the following documents to United Therapeutics Corporation or designee prior to study start: the signature page of the protocol, IRB/IEC Composition and Roster, IRB/IEC protocol and informed consent form approval letters, Form FDA 1572, Financial Disclosure Form, and Curriculum Vitae of study staff listed on the Form FDA 1572.

12.5 SUBJECT CONFIDENTIALITY

Every effort will be made to keep medical information confidential. United Therapeutics Corporation, the FDA or other regulatory bodies, and the IRB/ethics committee governing this study may inspect the medical records of any subject involved in this study. The Investigator may release the subject's medical records to employees or agents of the Sponsor, the IRB/ethics committee or the FDA or appropriate local regulatory agencies for purposes of checking the accuracy of the data. A number will be assigned to all subjects, and any report published will not identify the subject's name.

13 ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 PROTOCOL AMENDMENTS AND STUDY TERMINATION

Protocol amendments that could potentially adversely affect the safety of participating subjects or that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of subjects treated, or subject selection criteria may be made only after consultation between United Therapeutics Corporation or its designee and the Investigator.

All protocol amendments must be submitted to and approved by the appropriate regulatory authorities and IRB/EC prior to implementation.

A report documenting study termination must also be submitted to and acknowledged by the appropriate IRB/EC for each study site.

At the end of the study, where applicable, a final report will be provided to the local regulatory agencies.

13.2 STUDY DOCUMENTATION AND STORAGE

In accordance with federal/national regulations, ICH, and GCP guidelines, the Investigator must retain study records for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The Investigator must notify United Therapeutics Corporation before any disposal or change in location of study records.

13.3 STUDY MONITORING AND DATA COLLECTION

In accordance with federal/national regulations, ICH, and GCP guidelines, monitors for United Therapeutics Corporation or its designee will periodically contact the study site and could conduct on-site visits. During these visits, the monitor will at a minimum confirm ethical treatment of subjects, assess study progress, review data collected, conduct source document verification, verify drug accountability periodically, and identify any issues requiring resolution.

The Investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and his/her staff to the monitor to discuss any findings or any relevant issues.

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered in the eCRF.

To achieve this objective, the monitor's duties are to aid the Investigator and the Sponsor in the maintenance of complete, legible, well organized, and easily retrievable data. Before the enrollment of any subject in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the process for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents, and requests for clarification or correction may be made. After the eCRF data are entered by the site, the clinical research associate will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

13.4 ETHICAL CONDUCT OF THE STUDY

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

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15 APPENDICES

Appendix A. 6-Minute Walk Test and Borg Dyspnea Score

The 6-minute walk test (6MWT) should be administered by the same tester at each study site throughout the study.

The administration of the test and specifications of the testing area should be generally consistent with the American Thoracic Society guidelines and the usual practice of the study site. If the subject was assessed at Baseline using oxygen therapy, then all 6MWTs during the study should be conducted with the same oxygen flow rate and mode of administration.

Similarly, if the Baseline assessment was conducted without oxygen therapy, then subsequent assessments should also be conducted without oxygen therapy. Before each 6MWT, the subject should rest (seated) for at least 10 minutes.

The area used for the 6MWT should be premeasured at approximately 30 meters in length (but no shorter than 15 meters [16 yards or 50 feet] in length) and at least 2 to 3 meters in width. There must be no turns or significant curves to the 6MWT area. The length should be marked with gradations to ensure the accurate measurement of the distance walked. The area should be well ventilated. The tester may be at the starting end of the corridor or at the midpoint of the corridor with a stop-watch. Intermittent rest periods are allowed if the subject can no longer continue. If the subject needs to rest briefly, he/she may stand or sit and then begin again when he/she is sufficiently rested, but the clock will continue to run. At the end of 6 minutes, the tester will call "stop walking where you are" while simultaneously stopping the watch, and then measure the distance walked.

Tester Instructions to the Subject

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

"The purpose of this test is to find out how far you can walk in 6 minutes. You will start walking from this point and follow the hallway to the marker (eg, chair) at the end, turn

around and walk back. When you arrive back at the starting point you will walk back and forth again."

"You will walk back and forth as many times as you can in the 6-minute period. You may stop walking and rest if you need to rest. Just remain where you are until you can walk again. However, the most important thing about the test is that you cover as much ground as you possibly can during the 6 minutes. I will tell you the time, and I will let you know when the 6 minutes are up. When I say STOP, please stand right where you are."

After these instructions are given to the subject, the person administering the test will then ask:

"Do you have any questions about the test?"

The person administering the test will then start the test by saying the following to the subject:

"Are you ready?"
"Start walking when I say 'Go.'"

The person administering the test will tell the subject the time at each minute by saying:

"You have 5 minutes to go."
"You have 4 minutes to go."
"You have 3 minutes to go."
"You have 2 minutes to go."
"You have 1 minute to go."

At 6 minutes, the person administering the test will tell the subject:

"Stop where you are."

No other instruction or encouragement will be given during the test. Eye contact with the subject should be avoided during the test.

Borg Dyspnea Score

Immediately after the walk, the person administering the test will obtain a rating of dyspnea using the Borg dyspnea scale. The person will use the following dialogue:

"I would like to use the following scale to describe how out of breath you are (scale shown to subject). This scale uses 0 for no shortness of breath at all and 10 is the worst shortness of breath you have ever had. Please point to a number that tells me how short of breath you feel right now."

BORG DYSPNEA SCORE

0	=	Nothing at all	
0.5	=	Very, very light	(Just Noticeable)
1	=	Very light	
2	=	Light	(Weak)
3	=	Moderate	
4	=	Somewhat heavy	
5	=	Heavy	(Strong)
6	=		
7	=	Very heavy	
8	=		
9	=		
10	=	Very, very heavy	(Almost Maximal)

Appendix B. World Health Organization Functional Classification for Pulmonary Hypertenstion

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

Class II: Subjects with pulmonary hypertension resulting in slight limitation of physical activity. These subjects are comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class III: Subjects with pulmonary hypertension resulting in marked limitation of physical activity. These subjects are comfortable at rest. Ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class IV: Subjects with pulmonary hypertension with inability to carry out any physical activity without symptoms. These subjects manifest signs of right heart failures. Dyspnea and/or fatigue could be present even at rest. Discomfort is increased by any physical activity.

Appendix C. Guidelines and Definitions for Recording Adverse Events

The Investigator or a designated member of his/her staff will probe every subject for any adverse events that could have occurred. The Investigator should always ask the same question when conducting the verbal probe to ensure uniformity between subjects. The Investigator should ask:

"How are you doing (feeling)?"

Based on the subject's response to this question, the Investigator should ask additional questions relevant to the specific complaint such as:

"How severe is/was the symptom?"
"How often did the symptom occur?"
"How long did the symptom last?"

It is the Investigator's responsibility to review the results of all diagnostic and laboratory tests as they become available and ascertain if there is a clinically significant change from Baseline. If the results are determined to be a clinically significant change from Baseline, it should be reported as an adverse event. The Investigator can repeat the diagnostic process or laboratory test or request additional tests to verify the results of the original tests. When possible, a diagnosis associated with the subject's abnormality should be used as the reported adverse event.

Using provided definitions, the Investigator will then:

1. Rate the intensity and seriousness of the adverse event
2. Estimate the causality of the adverse event to study drug
3. Note actions taken to counteract the adverse event

Definitions of Intensity, Seriousness, Causality, Action Taken, and Outcome

Intensity

An assessment of the relative intensity (severity) of an adverse event is based on the Investigator's clinical judgement. The maximum intensity encountered during the evaluation

period should be checked. The assessment of intensity should be independent of the assessment of the seriousness of the adverse event.

Seriousness

A serious adverse event (SAE) is one that represents an actual or potential significant hazard. This includes, but is not limited to, an event that is fatal, life-threatening, permanently or severely disabling, requires or prolongs inpatient hospitalization*, is a congenital abnormality (offspring of subject), or is medically significant (important medical events that may not result in death, be life-threatening, or require hospitalization can be considered an SAE when, based upon appropriate medical judgment, they could jeopardize the subject and could require medical or surgical intervention to prevent one of the outcomes listed in the definition).

*Hospitalizations that would not be considered SAEs include those for:

- Routine treatment or monitoring of the study indication not associated with any deterioration in condition (eg, hospitalization for a routine right heart catheterization).
- Treatment which was elective or preplanned, for a pre-existing condition not associated with any deterioration in condition (eg, preplanned operation which does not lead to further complications, etc).
- Treatment of any emergency, in an outpatient setting for an event not fulfilling any of the definitions of seriousness as listed above and not resulting in hospital admission.

Causality

An estimate of causality between a specified adverse event and the study drug is made by the Investigator. Several factors should be considered when determining causality. These factors include temporal relationship and response to withdrawal or reintroduction of the study drug.

Definitions of the causality categories are as follows:

- NOT RELATED – There is not a temporal relationship to study drug administration (too early, or late, or study drug not taken), or there is a reasonable causal relationship between another drug, or concurrent disease and the SAE, or any of the following:
  - An event that precedes the first administration of study drug
  - An event for which the cause is clearly related to an external event
  - Temporal relationship to study drug is atypical

  - Is readily explained by an intercurrent illness AND has an expected level of severity, duration and resolution
    - An alternative explanation (concomitant drug, intercurrent illness) is likely
- POSSIBLE – There is a reasonable causal relationship between the study drug and the SAE. Dechallenge information is lacking or unclear, study drug administration was not modified in response to the SAE, or any of the following:
  - Has a reasonable temporal relationship to study drug
  - The event has a plausible biological link to the activity of the study drug
    - Is unlikely to be related to an intercurrent illness or has an unexpected degree of severity, duration, or complication
- PROBABLE – There is a reasonable causal relationship between the study drug and the SAE. The event responds to dechallenge – the event resolves or improves with modification of the study drug administration. Rechallenge (the original study drug was restarted) is not required, or any of the following:
  - Has a reasonable temporal relationship to study drug
  - The event has a plausible biologic link to the activity of the study drug
  - Not readily explained by an intercurrent illness
  - Not readily explained by external event
  - Improves on discontinuation of study drug
    - If study drug has been discontinued, could recur or reintroduction of study drug

Action Taken

STUDY DRUG DOSE MODIFICATION

- Dose Not Changed – The dose or regimen of the study drug was not changed
- Dose Increased – The dose or regimen of study drug was increased
- Dose Decreased – The dose or regimen of study drug was decreased
- Drug Interrupted – Administration of the study drug was stopped temporarily
- Drug Withdrawn – Administration of the study drug was stopped permanently and not restarted
- Unknown – Changes to the administration of the study drug cannot be determined.
- Not Applicable

NOTE: Only the last study drug action should be recorded in the eCRF. For example, if the study drug is withdrawn and then the decision is made to restart, the dose modification of "Drug interrupted" should be reported on the SAE form.

Outcome

- Fatal – The study subject died.
- Not Recovered/Not Resolved – The adverse event was ongoing at the time of death or at the time the subject was lost to follow up.
- Recovered/Resolved – The adverse event resolved.
- Recovered/Resolved with Sequelae – The adverse event is considered resolved; however, there is residual sequelae. Some events do not return to baseline, such as metastasis or progression of disease; however, once these events are determined by the Investigator to be stable or chronic, the Investigator may consider the event to be resolved or resolved with sequelae.
- Recovering/Resolving – The adverse event is improving but is not yet completely recovered/resolved.
- Unknown – The outcome of the adverse event cannot be determined.

Appendix D. Clinical Laboratory Parameters

Serum Chemistry	Hematology	Other
Sodium Potassium Chloride Bicarbonate/CO2 Blood urea nitrogen/urea Albumin Alkaline phosphatase Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Gamma-glutamyl transferase (GGT) Total bilirubin Indirect bilirubin Direct bilirubin Creatinine	Red blood cell count Hemoglobin Hematocrit Platelet count White blood cell count Prothrombin time/International Normalized Ratio CD4 count (for subjects with human immunodeficiency virus [HIV])	NT-proBNP (serum) Urine pregnancy test (for female subjects of childbearing potential)

NT-proBNP, N-terminal pro-brain natriuretic peptide

Tests by Study Visit

Study Visit	Clinical Labs
Screening	Chemistry, hematology, NT-proBNP, urine pregnancy test (for female subjects of childbearing potential), CD4 count (for subjects with HIV)
Baseline	Chemistry, hematology, NT-proBNP, urine pregnancy test (for female subjects of childbearing potential), and optional pharmacogenomics (genetic/RNA) and biomarker sample
Transition Visit	Chemistry, hematology, NT-proBNP, urine pregnancy test (for female subjects of childbearing potential), and biomarker testing in addition to scheduled testing for that study visit
Week 4	Urine pregnancy test (for female subjects of childbearing potential)
Week 8	Urine pregnancy test (for female subjects of childbearing potential)
Week 12	Urine pregnancy test (for female subjects of childbearing potential)
Week 16/Early Study Withdrawal	Chemistry, hematology, NT-proBNP, urine pregnancy test (for female subjects of childbearing potential), and optional biomarker sample

HIV, human immunodeficiency virus; NT-proBNP, N-terminal pro-brain natriuretic peptide; RNA, ribonucleic acid

Appendix E. AE Bothersome Survey

Investigators will ask subjects about the prostanoid-related effects they experienced using the AE Bothersome Survey. For this study, adverse events of interest include headache, diarrhea, nausea, flushing, jaw pain, extremity pain, and vomiting. Scores will be captured at the time points listed in Table 3-1. The Investigator will begin with Question 1, asking the subject about the AEs listed in the left-most column, and proceed to Question 2 and Question 3 for any AEs experienced by the subject. This questionnaire may be used to guide AE assessment and conversations about AEs that a subject is experiencing. Events captured by the AE Bothersome Survey should only be recorded as an AE and should only be captured as an SAE if the event is unusual with respect to intensity, frequency, or duration as compared with symptoms in the subject's medical history (see section 9.1).

AE Bothersome Survey							
	Question 1		**Question 2**				**Question 3**
	"Have you experienced this health problem or medication side effect in the past week?" (Please circle *yes* or *no*. If *yes*, proceed to Question 2 and Question 3.)		"For this health problem or medication side effect that you experienced, how bothersome has it been for you during the last week using the following scale?" 1 – bothers me a lot 2 – bothers me some 3 – bothers me a little 4 – not at all bothersome (Please circle one number and proceed to Question 3.)				"For this health problem or medication side effect that you experienced, how many days in the past week did you experience it?" (Please circle a number from 1 to 7.)
Headache	Yes	No	1	2	3	4	1 2 3 4 5 6 7
Diarrhea	Yes	No	1	2	3	4	1 2 3 4 5 6 7
Nausea	Yes	No	1	2	3	4	1 2 3 4 5 6 7
Flushing	Yes	No	1	2	3	4	1 2 3 4 5 6 7
Jaw pain	Yes	No	1	2	3	4	1 2 3 4 5 6 7
Extremity pain	Yes	No	1	2	3	4	1 2 3 4 5 6 7
Vomiting	Yes	No	1	2	3	4	1 2 3 4 5 6 7

Appendix F. Cockcroft-Gault Equation and Child-Pugh Score

Cockcroft-Gault Equation

CrCl (mL/min) = [(140 - age) x AjBW (kg)] / (SCr [mg/dL] x 72)

Note: multiply results by 0.85 for females.

Calculation of adjusted body weight in kg:

AjBW = IBW + 0.4(ABW - IBW)

Calculation of ideal body weight in kg:

Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet

Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet

Abbreviations: CrCl – creatinine clearance; AjBW – adjusted body weight; ABW – actual body weight; IBW – ideal body weight; SCr – serum creatinine

Child-Pugh Score

Parameter	Points		
	1	2	3
Hepatic encephalopathy	None (hepatic encephalopathy is absent)	Stage I to II (mild or suppressed with medication)	Stage III to IV (severe or refractory)
Ascites	None (ascites is absent)	Mild-moderate (suppressed with medication)	Moderate-severe (refractory)
Total bilirubin µmol/L (mg/dL)	<34 (<2)	34 to 50 (2 to 3)	>50 (>3)
Serum albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Prothrombin time(s)/ International Normalized Ratio	<4 (<1.7)	4 to 6 (1.71 to 2.20)	>6 (>2.20)

Class A (mild) = 5 to 6 points

Class B (moderate) = 7 to 9 points

Class C (severe) = 10 to 15 points

Appendix G. Treatment Satisfaction Questionnaire for Medication (TSQM) (Version 1.4)

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last two to three weeks, or since you last used it*. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

   ☐ 1 Extremely Dissatisfied
   ☐ 2 Very Dissatisfied
   ☐ 3 Dissatisfied
   ☐ 4 Somewhat Satisfied
   ☐ 5 Satisfied
   ☐ 6 Very Satisfied
   ☐ 7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

   ☐ 1 Extremely Dissatisfied
   ☐ 2 Very Dissatisfied
   ☐ 3 Dissatisfied
   ☐ 4 Somewhat Satisfied
   ☐ 5 Satisfied
   ☐ 6 Very Satisfied
   ☐ 7 Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

   ☐ 1 Extremely Dissatisfied
   ☐ 2 Very Dissatisfied
   ☐ 3 Dissatisfied
   ☐ 4 Somewhat Satisfied
   ☐ 5 Satisfied
   ☐ 6 Very Satisfied
   ☐ 7 Extremely Satisfied

4. As a result of taking this medication, do you experience any side effects at all?

   ☐ 1 Yes
   ☐ 0 No (if No, then please skip to Question 9)

5. How bothersome are the side effects of the medication you take to treat your condition?

- ☐ 1 Extremely Bothersome
- ☐ 2 Very Bothersome
- ☐ 3 Somewhat Bothersome
- ☐ 4 A Little Bothersome
- ☐ 5 Not at All Bothersome

6. To what extent do the side effects interfere with your physical health and ability to function (ie, strength, energy levels, etc)?

- ☐ 1 A Great Deal
- ☐ 2 Quite a Bit
- ☐ 3 Somewhat
- ☐ 4 Minimally
- ☐ 5 Not at All

7. To what extent do the side effects interfere with your mental function (ie, ability to think clearly, stay awake, etc)?

- ☐ 1 A Great Deal
- ☐ 2 Quite a Bit
- ☐ 3 Somewhat
- ☐ 4 Minimally
- ☐ 5 Not at All

8. To what degree have medication side effects affected your overall satisfaction with the medication?

- ☐ 1 A Great Deal
- ☐ 2 Quite a Bit
- ☐ 3 Somewhat
- ☐ 4 Minimally
- ☐ 5 Not at All

9. How easy or difficult is it to use the medication in its current form?

- ☐ 1 Extremely Difficult
- ☐ 2 Very Difficult
- ☐ 3 Difficult
- ☐ 4 Somewhat Easy
- ☐ 5 Easy
- ☐ 6 Very Easy
- ☐ 7 Extremely Easy

10. How easy or difficult is it to plan when you will use the medication each time?

- ☐ 1 Extremely Difficult
- ☐ 2 Very Difficult
- ☐ 3 Difficult
- ☐ 4 Somewhat Easy
- ☐ 5 Easy
- ☐ 6 Very Easy
- ☐ 7 Extremely Easy

11. How convenient or inconvenient is it to take the medication as instructed?

- ☐ 1 Extremely Inconvenient
- ☐ 2 Very Inconvenient
- ☐ 3 Inconvenient
- ☐ 4 Somewhat Convenient
- ☐ 5 Convenient
- ☐ 6 Very Convenient
- ☐ 7 Extremely Convenient

12. Overall, how confident are you that taking this medication is a good thing for you?

- ☐ 1 Not at All Confident
- ☐ 2 A Little Confident
- ☐ 3 Somewhat Confident
- ☐ 4 Very Confident
- ☐ 5 Extremely Confident

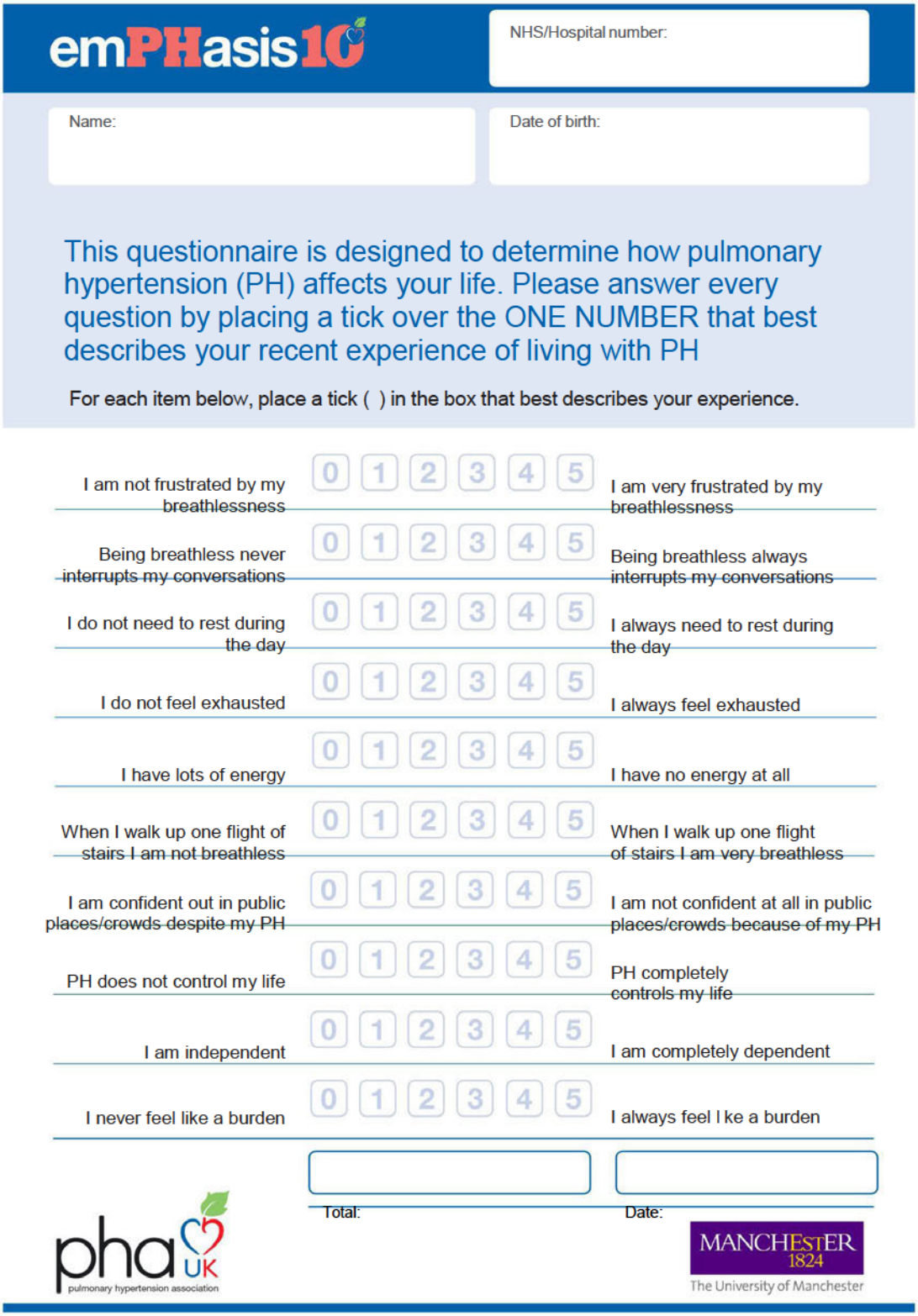
13. How certain are you that the good things about your medication outweigh the bad things?

- ☐ 1 Not at All Certain
- ☐ 2 A Little Certain
- ☐ 3 Somewhat Certain
- ☐ 4 Very Certain
- ☐ 5 Extremely Certain

14. Taking all things into account, how satisfied or dissatisfied are you with this medication?

- ☐ 1 Extremely Dissatisfied
- ☐ 2 Very Dissatisfied
- ☐ 3 Dissatisfied
- ☐ 4 Somewhat Satisfied
- ☐ 5 Satisfied
- ☐ 6 Very Satisfied
- ☐ 7 Extremely Satisfied

Appendix H. emPHasis-10 Questionnaire



emPHasis10

NHS/Hospital number:

Name:

Date of birth:

This questionnaire is designed to determine how pulmonary hypertension (PH) affects your life. Please answer every question by placing a tick over the ONE NUMBER that best describes your recent experience of living with PH

For each item below, place a tick ( ) in the box that best describes your experience.

I am not frustrated by my breathlessness	0 1 2 3 4 5	I am very frustrated by my breathlessness
Being breathless never interrupts my conversations	0 1 2 3 4 5	Being breathless always interrupts my conversations
I do not need to rest during the day	0 1 2 3 4 5	I always need to rest during the day
I do not feel exhausted	0 1 2 3 4 5	I always feel exhausted
I have lots of energy	0 1 2 3 4 5	I have no energy at all
When I walk up one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up one flight of stairs I am very breathless
I am confident out in public places/crowds despite my PH	0 1 2 3 4 5	I am not confident at all in public places/crowds because of my PH
PH does not control my life	0 1 2 3 4 5	PH completely controls my life
I am independent	0 1 2 3 4 5	I am completely dependent
I never feel like a burden	0 1 2 3 4 5	I always feel I ke a burden

Total:

Date:

pha UK pulmonary hypertension association

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Appendix I. Transition Schedule Examples

3 Days Duration

3 Days Duration for a 70 kg Subject at a Remodulin Dose of 30 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg)
	Day 1 (0-24 hours)	
Morning	30	0
Afternoon	26	0.625
Evening	22	1.375
	Day 2 (24-48 hours)	
Morning	18	2
Afternoon	14	2.625
Evening	10	3.125
	Day 3 (48-72 hours)	
Morning	6	3.75
Afternoon	3	4.375
Evening	0	5

3 Days Duration for a 40 kg Subject at a Remodulin Dose of 30 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg)
	Day 1 (0-24 hours)	
Morning	30	0
Afternoon	26	0.375
Evening	22	0.75
	Day 2 (24-48 hours)	
Morning	18	1.125
Afternoon	14	1.5
Evening	10	2
	Day 3 (48-72 hours)	
Morning	6	2.25
Afternoon	3	2.5
Evening	0	2.875

3 Days Duration for a 120 kg Subject at a Remodulin Dose of 30 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg)
	Day 1 (0-24 hours)	
Morning	30	0
Afternoon	26	1.125
Evening	22	2.25
	Day 2 (24-48 hours)	
Morning	18	3.5
Afternoon	14	4.625
Evening	10	5.75
	Day 3 (48-72 hours)	
Morning	6	6.875
Afternoon	3	7.75
Evening	0	8.625

3 Days Duration for a 70 kg Subject at a Remodulin Dose of 20 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg)
	Day 1 (0-24 hours)	
Morning	20	0
Afternoon	18	0.125
Evening	15	0.25
	Day 2 (24-48 hours)	
Morning	13	0.375
Afternoon	10	0.5
Evening	8	0.625
	Day 3 (48-72 hours)	
Morning	5	0.75
Afternoon	2	0.875
Evening	0	1

3 Days Duration for a 40 kg Subject at a Remodulin Dose of 20 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg)
	Day 1 (0-24 hours)	
Morning	20	0
Afternoon	18	0.25
Evening	15	0.5
	Day 2 (24-48 hours)	
Morning	13	0.625
Afternoon	10	1
Evening	8	1.125
	Day 3 (48-72 hours)	
Morning	5	1.5
Afternoon	2	1.75
Evening	0	2

3 Days Duration for a 120 kg Subject at a Remodulin Dose of 20 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg)
	Day 1 (0-24 hours)	
Morning	20	0
Afternoon	18	0.625
Evening	15	1.5
	Day 2 (24-48 hours)	
Morning	13	2
Afternoon	10	2.875
Evening	8	3.5
	Day 3 (48-72 hours)	
Morning	5	4.375
Afternoon	2	5.125
Evening	0	5.75

3 Days Duration for a 70 kg Subject at a Remodulin Dose of 40 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg)
	Day 1 (0-24 hours)	
Morning	40	0
Afternoon	35	0.875
Evening	30	1.625
	Day 2 (24-48 hours)	
Morning	25	2.5
Afternoon	20	3.375
Evening	15	4.25
	Day 3 (48-72 hours)	
Morning	10	5
Afternoon	5	5.875
Evening	0	6.75

3 Days Duration for a 40 kg Subject at a Remodulin Dose of 40 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg)
	Day 1 (0-24 hours)	
Morning	40	0
Afternoon	35	0.5
Evening	30	1
	Day 2 (24-48 hours)	
Morning	25	1.5
Afternoon	20	1.875
Evening	15	2.375
	Day 3 (48-72 hours)	
Morning	10	2.875
Afternoon	5	3.375
Evening	0	3.875

3 Days Duration for a 120 kg Subject at a Remodulin Dose of 40 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg)
	Day 1 (0-24 hours)	
Morning	40	0
Afternoon	35	1.5
Evening	30	2.875
	Day 2 (24-48 hours)	
Morning	25	4.375
Afternoon	20	5.75
Evening	15	7.25
	Day 3 (48-72 hours)	
Morning	10	8.625
Afternoon	5	10
Evening	0	11.5

5 Days Duration

5 Days Duration for a 70 kg Subject at a Remodulin Dose of 30 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg)
Day 1 (0-24 hours)		
Morning	30	0
Afternoon	28	0.375
Evening	26	0.625
Day 2 (24-48 hours)		
Morning	24	1
Afternoon	22	1.375
Evening	20	1.625
Day 3 (48-72 hours)		
Morning	17	2.125
Afternoon	14	2.75
Evening	12	3
Day 4 (72-96 hours)		
Morning	10	3.375
Afternoon	8	3.75
Evening	6	4
Day 5 (96-120 hours)		
Morning	4	4.375
Afternoon	2	4.75
Evening	0	5

5 Days Duration for a 40 kg Subject at a Remodulin Dose of 30 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg)
Day 1 (0-24 hours)		
Morning	30	0
Afternoon	28	0.25
Evening	26	0.375
Day 2 (24-48 hours)		
Morning	24	0.625
Afternoon	22	0.75
Evening	20	1
Day 3 (48-72 hours)		
Morning	17	1.25
Afternoon	14	1.5
Evening	12	1.75
Day 4 (72-96 hours)		
Morning	10	2
Afternoon	8	2.125
Evening	6	2.25
Day 5 (96-120 hours)		
Morning	4	2.5
Afternoon	2	2.675
Evening	0	2.875

5 Days Duration for a 120 kg Subject at a Remodulin Dose of 30 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg)
Day 1 (0-24 hours)		
Morning	30	0
Afternoon	28	0.625
Evening	26	1.125
Day 2 (24-48 hours)		
Morning	24	1.75
Afternoon	22	2.25
Evening	20	2.875
Day 3 (48-72 hours)		
Morning	17	3.75
Afternoon	14	4.625
Evening	12	5.125
Day 4 (72-96 hours)		
Morning	10	5.75
Afternoon	8	6.375
Evening	6	6.875
Day 5 (96-120 hours)		
Morning	4	7.5
Afternoon	2	8
Evening	0	8.625

5 Days Duration for a 70 kg Subject at a Remodulin Dose of 20 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg)
Day 1 (0-24 hours)		
Morning	20	0
Afternoon	18	0.375
Evening	17	0.5
Day 2 (24-48 hours)		
Morning	16	0.625
Afternoon	14	1
Evening	13	1.125
Day 3 (48-72 hours)		
Morning	11	1.5
Afternoon	10	1.625
Evening	8	2
Day 4 (72-96 hours)		
Morning	7	2.125
Afternoon	5	2.5
Evening	4	2.625
Day 5 (96-120 hours)		
Morning	2	3
Afternoon	1	3.25
Evening	0	3.375

5 Days Duration for a 40 kg Subject at a Remodulin Dose of 20 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg)
Day 1 (0-24 hours)		
Morning	20	0
Afternoon	18	0.125
Evening	17	0.25
Day 2 (24-48 hours)		
Morning	16	0.375
Afternoon	14	0.5
Evening	13	0.675
Day 3 (48-72 hours)		
Morning	11	0.875
Afternoon	10	1
Evening	8	1.125
Day 4 (72-96 hours)		
Morning	7	1.25
Afternoon	5	1.375
Evening	4	1.5
Day 5 (96-120 hours)		
Morning	2	1.625
Afternoon	1	1.75
Evening	0	2

5 Days Duration for a 120 kg Subject at a Remodulin Dose of 20 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg)
Day 1 (0-24 hours)		
Morning	20	0
Afternoon	18	0.5
Evening	17	0.875
Day 2 (24-48 hours)		
Morning	16	1.125
Afternoon	14	1.75
Evening	13	2
Day 3 (48-72 hours)		
Morning	11	2.5
Afternoon	10	2.875
Evening	8	3.5
Day 4 (72-96 hours)		
Morning	7	3.75
Afternoon	5	4.375
Evening	4	4.625
Day 5 (96-120 hours)		
Morning	2	5.125
Afternoon	1	5.5
Evening	0	5.75

5 Days Duration for a 70 kg Subject at a Remodulin Dose of 40 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg)
Day 1 (0-24 hours)		
Morning	40	0
Afternoon	37	0.5
Evening	34	1
Day 2 (24-48 hours)		
Morning	31	1.5
Afternoon	28	2
Evening	26	2.375
Day 3 (48-72 hours)		
Morning	23	2.875
Afternoon	20	3.325
Evening	17	3.875
Day 4 (72-96 hours)		
Morning	15	4.25
Afternoon	12	4.75
Evening	9	5.25
Day 5 (96-120 hours)		
Morning	6	5.75
Afternoon	3	6.25
Evening	0	6.75

5 Days Duration for a 40 kg Subject at a Remodulin Dose of 40 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg)
Day 1 (0-24 hours)		
Morning	40	0
Afternoon	37	0.25
Evening	34	0.625
Day 2 (24-48 hours)		
Morning	31	0.875
Afternoon	28	1.125
Evening	26	1.375
Day 3 (48-72 hours)		
Morning	23	1.625
Afternoon	20	1.875
Evening	17	2.25
Day 4 (72-96 hours)		
Morning	15	2.375
Afternoon	12	2.625
Evening	9	3
Day 5 (96-120 hours)		
Morning	6	3.25
Afternoon	3	3.5
Evening	0	3.875

5 Days Duration for a 120 kg Subject at a Remodulin Dose of 40 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg)
Day 1 (0-24 hours)		
Morning	40	0
Afternoon	37	0.875
Evening	34	1.75
Day 2 (24-48 hours)		
Morning	31	2.625
Afternoon	28	3.5
Evening	26	4
Day 3 (48-72 hours)		
Morning	23	4.875
Afternoon	20	5.75
Evening	17	6.625
Day 4 (72-96 hours)		
Morning	15	7.25
Afternoon	12	8
Evening	9	8.875
Day 5 (96-120 hours)		
Morning	6	9.75
Afternoon	3	10.625
Evening	0	11.5

9 Days Duration

9 Days Duration for a 70 kg Subject at a Remodulin Dose of 30 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg) TID
Day 1	30	0
Day 2	26	0.625
Day 3	22	1.375
Day 4	18	2
Day 5	14	2.625
Day 6	10	3.125
Day 7	6	3.75
Day 8	3	4.375
Day 9	0	5

9 Days Duration for a 40 kg Subject at a Remodulin Dose of 30 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg) TID
Day 1	30	0
Day 2	26	0.375
Day 3	22	0.75
Day 4	18	1.125
Day 5	14	1.5
Day 6	10	2
Day 7	6	2.25
Day 8	3	2.5
Day 9	0	2.875

9 Days Duration for a 120 kg Subject at a Remodulin Dose of 30 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg) TID
Day 1	30	0
Day 2	26	1.125
Day 3	22	2.25
Day 4	18	3.5
Day 5	14	4.625
Day 6	10	5.75
Day 7	6	6.875
Day 8	3	7.75
Day 9	0	8.625

9 Days Duration for a 70 kg Subject at a Remodulin Dose of 20 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg) TID
Day 1	20	0
Day 2	18	0.375
Day 3	15	0.875
Day 4	13	1.125
Day 5	10	1.625
Day 6	8	2
Day 7	5	2.5
Day 8	2	3
Day 9	0	3.325

9 Days Duration for a 40 kg Subject at a Remodulin Dose of 20 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg) TID
Day 1	20	0
Day 2	18	0.25
Day 3	15	0.5
Day 4	13	0.625
Day 5	10	1
Day 6	8	1.125
Day 7	5	1.5
Day 8	2	1.75
Day 9	0	2

9 Days Duration for a 120 kg Subject at a Remodulin Dose of 20 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg) TID
Day 1	20	0
Day 2	18	0.625
Day 3	15	1.5
Day 4	13	2
Day 5	10	2.85
Day 6	8	3.5
Day 7	5	4.375
Day 8	2	5.125
Day 9	0	5.75

9 Days Duration for a 70 kg Subject at a Remodulin Dose of 40 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg) TID
Day 1	40	0
Day 2	35	0.875
Day 3	30	1.625
Day 4	25	2.5
Day 5	20	3.375
Day 6	15	4.25
Day 7	10	5
Day 8	5	5.875
Day 9	0	6.75

9 Days Duration for a 40 kg Subject at a Remodulin Dose of 40 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg) TID
Day 1	40	0
Day 2	35	0.5
Day 3	30	1
Day 4	25	1.5
Day 5	20	2
Day 6	15	2.375
Day 7	10	2.875
Day 8	5	3.375
Day 9	0	3.875

9 Days Duration for a 120 kg Subject at a Remodulin Dose of 40 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg) TID
Day 1	40	0
Day 2	35	1.5
Day 3	30	2.875
Day 4	25	4.375
Day 5	20	5.75
Day 6	15	7.25
Day 7	10	8.625
Day 8	5	10
Day 9	0	11.5

17 Days Duration

17 Days Duration for a 70 kg Subject at a Remodulin Dose of 30 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg) TID
Day 1	30	0
Day 3	26	0.625
Day 5	22	1.375
Day 7	18	2
Day 9	14	2.625
Day 11	10	3.125
Day 13	6	3.75
Day 15	3	4.375
Day 17	0	5

17 Day Duration for a 40 kg Subject at a Remodulin Dose of 30 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg) TID
Day 1	30	0
Day 3	26	0.375
Day 5	22	0.75
Day 7	18	1.125
Day 9	14	1.5
Day 11	10	2
Day 13	6	2.25
Day 15	3	2.5
Day 17	0	2.875

17 Days Duration for a 120 kg Subject at a Remodulin Dose of 30 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg) TID
Day 1	30	0
Day 3	26	1.125
Day 5	22	2.25
Day 7	18	3.5
Day 9	14	4.625
Day 11	10	5.75
Day 13	6	6.875
Day 15	3	7.75
Day 17	0	8.625

17 Days Duration for a 70 kg Subject at a Remodulin Dose of 20 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg) TID
Day 1	20	0
Day 3	18	0.375
Day 5	15	0.875
Day 7	13	1.125
Day 9	10	1.625
Day 11	8	2
Day 13	5	2.5
Day 15	2	3
Day 17	0	3.325

17 Day Duration for a 40 kg Subject at a Remodulin Dose of 20 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg) TID
Day 1	20	0
Day 3	18	0.25
Day 5	15	0.5
Day 7	13	0.625
Day 9	10	1
Day 11	8	1.125
Day 13	5	1.5
Day 15	2	1.75
Day 17	0	2

17 Days Duration for a 120 kg Subject at a Remodulin Dose of 20 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg) TID
Day 1	20	0
Day 3	18	0.625
Day 5	15	1.5
Day 7	13	2
Day 9	10	2.85
Day 11	8	3.5
Day 13	5	4.375
Day 15	2	5.125
Day 17	0	5.75

17 Days Duration for a 70 kg Subject at a Remodulin Dose of 40 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg) TID
Day 1	40	0
Day 3	35	0.875
Day 5	30	1.625
Day 7	25	2.5
Day 9	20	3.375
Day 11	15	4.25
Day 13	10	5
Day 15	5	5.875
Day 17	0	6.75

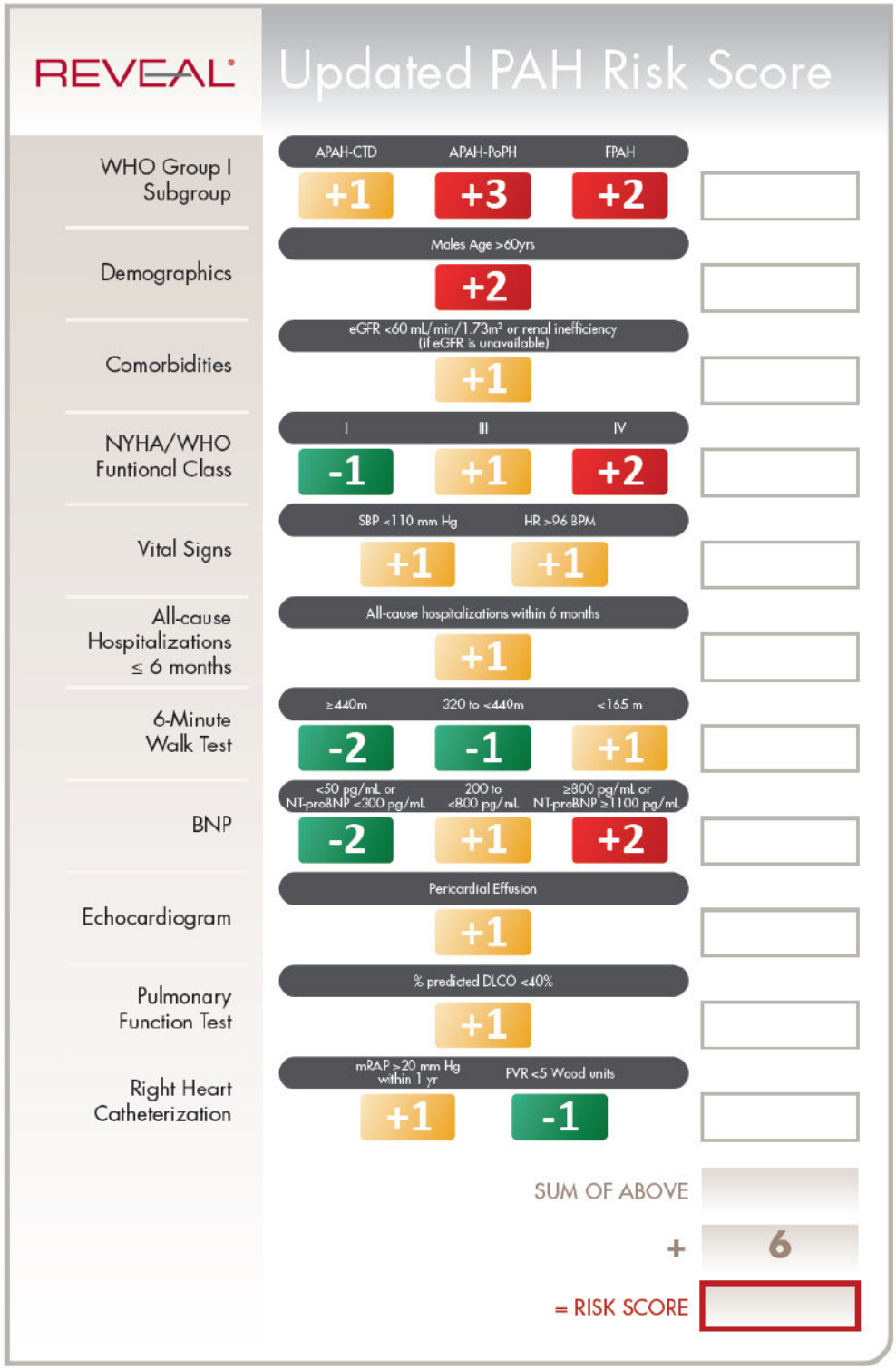
17 Days Duration for a 40 kg Subject at a Remodulin Dose of 40 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg) TID
Day 1	40	0
Day 3	35	0.5
Day 5	30	1
Day 7	25	1.5
Day 9	20	2
Day 11	15	2.375
Day 13	10	2.875
Day 15	5	3.375
Day 17	0	3.875

17 Days Duration for a 120 kg Subject at a Remodulin Dose of 40 ng/kg/min

Transition Day	Remodulin Dose (ng/kg/min)	Orenitram Dose (mg) TID
Day 1	40	0
Day 3	35	1.5
Day 5	30	2.875
Day 7	25	4.375
Day 9	20	5.75
Day 11	15	7.25
Day 13	10	8.625
Day 15	5	10
Day 17	0	11.5

Appendix J. REVEAL 2.0 Risk Score



Instructions:

Above is the updated REVEAL 2.0 risk score calculator, which has been modified from the original to refine scoring for several risk variables (Benza 2010; Benza 2018). Subjects with a score of 10 or higher at Screening are ineligible for the study.

- At least 7 of the above 12 variables (with mRAP and PVR considered 2 separate variables within the Right Heart Catheterization) must be used to calculate a valid risk score.
- 3 of the ≥7 variables used for the calculation must include the Screening results for WHO Functional Class, NT-proBNP, and 6-Minute Walk Test.
- Additionally, vital signs (SBP and HR) and SCr (used to calculated eGFR) obtained at screening should be included in the risk score.
- Historical test results may be used to calculate the risk score:
  - A historical echocardiogram may be used if the echocardiogram was performed within 60 days of Screening. A score of +1 will be given for pericardial effusion that is graded as mild, moderate, or severe. A score of 0 will be given for trace pericardial effusion.
  - A historical pulmonary function test may be used if it was performed within 60 days of screening.
  - A historical right heart catheterization (RHC) should be used if it was performed within 180 days of Baseline and the subject has had no changes in their PAH medication regimen (ie, both dosing and drug) since the RHC. If the subject receives an RHC at their Screening visit, the Screening RHC should be used in the subject's REVEAL 2.0 score.