A Multicenter, Open-Label, 24-Week, Uncontrolled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Oral Treprostinil Extended Release Tablets Following Transition from Remodulin or Inhaled Prostacyclin Therapy or as Add-on to Current PAH Therapy in De Novo Prostacyclin Pediatric Subjects Aged 7 to 17 Years with Pulmonary Arterial Hypertension

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CONFIDENTIAL

UNITED THERAPEUTICS CORPORATION

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LIST OF CONTACTS FOR STUDY

Study Sponsor	**United Therapeutics Corp**. 55 TW Alexander Drive PO Box 14186 Research Triangle Park, NC 27709 USA [redacted] (Clinical Trial Leader) [redacted] [redacted] (Program Head) [redacted] [redacted] (Medical Monitor) [redacted]
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INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "A Multicenter, Open-Label, 24-Week, Uncontrolled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Oral Treprostinil Extended Release Tablets Following Transition from Remodulin or Inhaled Prostacyclin Therapy or as Add-on to Current PAH Therapy in De Novo Prostacyclin Pediatric Subjects Aged 7 to 17 Years with Pulmonary Arterial Hypertension," Amendment 2 (01 Sep 2016) and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on 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' Brochure for oral treprostinil (UT-15C; treprostinil diolamine) and acknowledge that review of the information contained in the Clinical Investigators' Brochure is a requirement for Investigators before using oral treprostinil in a clinical trial.

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

PROTOCOL SYNOPSIS

Title	A Multicenter, Open-Label, 24-Week, Uncontrolled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Oral Treprostinil Extended Release Tablets Following Transition from Remodulin or Inhaled Prostacyclin Therapy or as Add-on to Current PAH Therapy in De Novo Prostacyclin Pediatric Subjects Aged 7 to 17 Years with Pulmonary Arterial Hypertension
Study Phase	Phase II
Indication	Pulmonary Arterial Hypertension (PAH)
Primary Objective	To assess the safety and tolerability of oral treprostinil extended release tablets in three cohorts of pediatric subjects with PAH aged 7 to 17 years: • ***Cohort 1***: Subjects transitioning from intravenous (IV) or subcutaneous (SC) Remodulin® • ***Cohort 2***: Subjects transitioning from inhaled prostacyclin • ***Cohort 3***: As add-on to current PAH therapy in de novo prostacyclin subjects
Secondary Objective(s)	1) To assess the effect of oral treprostinil on the following (assessed in all cohorts): • Cardiopulmonary exercise testing (CPET) with progressive cycle ergometry • Symptoms of PAH • Panama functional classification • WHO functional classification • Six-minute walk distance (6MWD) (with oximetry and heart rate [HR] recovery monitoring) • Borg dyspnea score • Quality of life assessed via the Pediatric Quality of Life Inventory (PedsQL™) questionnaire • Plasma N-terminal pro-B-type natriuretic peptide (NT-Pro BNP) • Cardiac magnetic resonance imaging (cMRI) 2) To describe treprostinil pharmacokinetics (PK) in pediatric subjects with PAH aged 7 to 17 years.
Study Design	Multi-center, open-label, safety, tolerability and PK study of oral treprostinil in pediatric subjects with stable PAH aged 7 to 17 years who are, (1) transitioning from IV/SC Remodulin therapy; (2) transitioning from inhaled prostacyclin therapy; or (3) not currently receiving prostacyclin therapy.
Sample Size	Up to 40 pediatric subjects aged 7 to 17 years (25 transition [IV/SC Remodulin and inhaled] subjects and 15 de novo subjects)

Summary of Subject Eligibility Criteria	***All Cohorts:*** Eligible subjects are between 7 and 17 years of age, inclusive, and have a diagnosis of PAH as confirmed by a previous right heart catheterization (RHC). Panama functional classification IIIb and IV subjects will be excluded. All subjects must be optimally treated (as determined by the Investigator) with background PAH therapies (e.g., phosphodiesterase type 5 inhibitor [PDE-5i], endothelin receptor antagonist [ERA], soluble guanylate cyclase [sGC]) for at least 90 days and have been on a stable dose without changes (except documented weight based adjustments) for at least 30 days prior to the first dose of oral treprostinil. ***Cohort 1: Remodulin to Oral Treprostinil Transition*** Subjects must have been receiving IV/SC Remodulin for at least 90 days and at a stable dose for at least 30 days prior to the first dose of oral treprostinil. The IV/SC Remodulin dose will be between 25-75 ng/kg/min, inclusive, for the first five subjects enrolled in Cohort 1. Following a safety review by the Data Safety Monitoring Board (DSMB) after the first five Cohort 1 subjects have been enrolled and transitioned to oral treprostinil (study drug), the dose range may be expanded to 25-125 ng/kg/min, inclusive, for the remaining subjects. ***Cohort 2: Inhaled Prostacyclin to Oral Treprostinil Transition*** Subjects must have been receiving inhaled prostacyclin therapy for at least 90 days and at a stable dose for at least 30 days prior to the first dose of oral treprostinil. ***Cohort 3: Add-On to Current PAH Therapy in De Novo Prostacyclin*** Subjects must weigh at least 22 kg.

Drug Dosage and Formulation	***All Cohorts:*** All subjects will receive study drug (oral treprostinil extended release tablets). The tablets may be provided as 0.125, 0.25, 1, or 2.5 mg strengths. Oral treprostinil will be dosed three times daily (TID) or four times daily (QID) at the discretion of the Investigator, with food. Dosing will take place approximately every 6 to 8 hours for TID dosing, or approximately every 4 to 6 hours for QID dosing, with adjustments permitted based on the subject's lifestyle and schedule. Sudden dose escalation or reductions should be avoided as they may lead to intolerable adverse events (AEs) or worsening of PAH. Gradual dose titrations are recommended to reduce the risk to subjects. ***Cohort 1: IV/SC Remodulin to Oral Treprostinil Transition*** ***Dose Transition Schedule:*** Once all entry criteria have been met and Baseline assessments completed, subjects will begin transition in the hospital from IV/SC Remodulin to oral treprostinil with a goal for complete transition off of IV/SC Remodulin within five days of the start of the transition. If possible, Day 5 (or last day of hospital stay, if transition occurred in less than 4 days) should be reserved as an observational period for subjects successfully transitioned to oral treprostinil and no longer receiving IV/SC Remodulin. Subjects will be discharged from the hospital after they have transitioned off IV/SC Remodulin, reached their target oral treprostinil dose, or as the Investigator feels appropriate. If necessary or appropriate per Investigator discretion, subjects can prolong or complete the transition in an outpatient setting for a total transition time of up to four weeks. A cross titration will occur so that the dose of IV/SC Remodulin is decreased as the dose of oral treprostinil is increased. Once subjects have been transitioned off IV/SC Remodulin, the dose of oral treprostinil may continue to be modified/titrated to the appropriate optimal dose for that subject throughout the rest of the study. ***Cross Titration Dosing Guidelines:*** • IV/SC Remodulin should not be decreased more than 30 ng/kg/min within a 24 hour period • Oral treprostinil should be increased in proportion to Remodulin decreases and the subject's weight • IV/SC Remodulin doses should be adjusted (i.e., decreased) at the same time oral treprostinil dose is increased

	Cohort 2: Inhaled Prostacyclin to Oral Treprostinil Transition ***Dose Transition Schedule:*** Once all entry criteria have been met and Baseline assessments completed, dosing of oral treprostinil will be initiated at 0.125 mg TID or QID, at the discretion of the Investigator, with food. Dosing will take place approximately every 6 to 8 hours for TID dosing, or approximately every 4 to 6 hours for QID dosing, with adjustments permitted based on the subject's lifestyle and schedule. The first dose of 0.125 mg oral treprostinil should occur at the study site. Dose escalations may occur every 24 hours (following three or four consecutive doses, depending on TID or QID dosing, respectively) and should occur in increments of 0.125 mg TID or QID at the discretion of the Investigator during the first four weeks of the study as clinically indicated. Following four weeks of treatment, dose escalations may occur in either 0.125 mg or 0.25 mg increments every 24 hours, as tolerated. A cross titration will occur so that the doses of inhaled prostacyclin are decreased and the subject is fully transitioned off the inhaled prostacyclin by no later than Week 4. ***Cohort 3: Add-On to Current PAH Therapy in De Novo Prostacyclin*** ***Dose Schedule:*** Once all entry criteria have been met and Baseline assessments completed, dosing of oral treprostinil will be initiated at 0.125 mg TID or QID, at the discretion of the Investigator, with food. Dosing will take place approximately every 6 to 8 hours for TID dosing, or approximately every 4 to 6 hours for QID dosing, with adjustments permitted based on the subject's lifestyle and schedule. The first dose of oral treprostinil should be taken at the study site. Dose escalations may occur every 24 hours (following three or four consecutive doses depending on TID or QID dosing, respectively) and should occur in increments of 0.125 mg TID or QID at the discretion of the Investigator during the first four weeks of the study as clinically indicated. Following four weeks of treatment, dose escalations may occur in either 0.125 mg or 0.25 mg increments every 24 hours, as tolerated.
Control Group	None
Route of Administration	Oral
Procedures	Up to seven study visits will occur during the 24-week study at the following time points: Screening, Baseline, Week 0 (Cohort 1 only; inpatient hospital stay Days 1-5), Week 3 Week 6, Week 12, and Week 24.

Screening/Baseline (All Cohorts):

All subjects will be assessed for eligibility during the 28 day screening period. Baseline assessments can be conducted over five days (120 hours) prior to the first dose of oral treprostinil, to allow for scheduling of all activities. The Screening and Baseline visits may be combined if all entry criteria are satisfied and all assessments are completed within five days (120 hours) prior to the first dose of oral treprostinil. The following assessments will be performed: vital signs, physical examination, six-minute walk test (6MWT)/Borg dyspnea score, CPET, 12-lead ECG, Panama and WHO functional classification assessments, symptoms of PAH, PedsQL, NT-Pro BNP, cMRI, clinical laboratory assessments, and safety assessments. Females of child bearing potential will undergo a urine pregnancy test. In addition, all subjects in Cohort 1will undergo an 8-hour PK assessment, which may occur up to seven days prior to the first dose of oral treprostinil (study drug). Pharmacokinetic assessments at Baseline will not be conducted in Cohort 2 or Cohort 3 subjects.

Transition Phase (Cohort 1):

Within five days (120 hours) of beginning Baseline assessments Cohort 1 subjects will undergo an inpatient hospital stay lasting approximately five days (Week 0) to transition from IV/SC Remodulin to oral treprostinil. The target transition goal is no longer than five days and for the subject to be completely transitioned off IV/SC Remodulin prior to discharge from the hospital. Subjects will be discharged from the hospital after they have transitioned off IV/SC Remodulin, reached their target oral treprostinil dose, or as the Investigator feels appropriate. If necessary or appropriate per Investigator discretion, subjects can prolong or complete the transition in an outpatient setting for a total transition time of up to four weeks.

The maximum time to titrate off IV/SC Remodulin is four weeks from the start of the transition; if the subject is not fully transitioned by Week 4, they will be removed from the study. If the subject is in the hospital during one of the scheduled study visits, the assessments for that visit should be conducted as scheduled during the defined visit window.

Treatment Phase (Cohort 2 and 3):

Following completion of Baseline assessments, the first dose of 0.125 mg oral treprostinil should be taken at the study site. Dosing of oral treprostinil will be initiated at 0.125 mg TID or QID, at the discretion of the Investigator, with food. Dosing will take place

	approximately every 6 to 8 hours for TID dosing, or approximately every 4 to 6 hours for QID dosing, with adjustments permitted based on the subject's lifestyle and schedule. Dose changes should be conducted under appropriate medical supervision in consultation with the study site. ***Dose Optimization/Evaluation Phase (All Cohorts):*** ***Weeks 3, 6, and 12****:* Subjects will return to clinic for the following assessments: vital signs, 6MWT/Borg dyspnea score, Panama and WHO functional classification, symptoms of PAH, and safety assessments. At each visit, females of childbearing potential will undergo a urine pregnancy test. At Week 12, QOL (as measured by PedsQL Inventory) and clinical laboratory assessments, including NT-pro-BNP, will occur. ***Week 24 (or premature termination)****:* Subjects will return to the clinic for the following assessments: vital signs, physical examination, 6MWT/Borg dyspnea score, CPET, 12-lead ECG, Panama and WHO functional class, symptoms of PAH, PedsQL, NT-Pro BNP, cMRI, clinical laboratory assessments, and safety assessments. Females of child bearing potential will undergo a urine pregnancy test. In addition, all subjects will undergo an 8-hour PK assessment.
Stopping Criteria	Stopping Criteria: • Unplanned hospitalization as a result of worsening PAH • Clinically significant worsening in PAH symptoms or signs, which the Investigator feels requires a change of current therapy If one of these events occur within the four weeks following the first dose of oral treprostinil, the subject should be transitioned back to IV/SC Remodulin (for Cohort 1 subjects) and tapered off oral treprostinil, as appropriate, and discontinued from study. If any of these events occur after the first four weeks of the study, it is not required that a subject be removed from the study. The Investigator will determine whether it is safe for the subject to remain in the study. If two or more of the first five subjects in any cohort meet the stopping criteria, the data will be reviewed by the DSMB prior to enrolling additional subjects into that cohort.
Statistical Considerations	The study is not powered to test a null hypothesis. A sample size of 40 pediatric PAH subjects aged 7 to 17 years (25 transition [IV/SC Remodulin and inhaled] subjects and 15 de novo prostacyclin subjects) will enable a descriptive evaluation of the PK and an

	initial assessment of the safety and tolerability in this subject population for (1) transition from moderate to high doses of IV/SC Remodulin to oral treprostinil, (2) transition from inhaled prostacyclin to oral treprostinil, and (3) initiation of oral treprostinil as add-on therapy in de novo prostacyclin subjects. The safety and tolerability of transitioning subjects from IV/SC Remodulin to oral treprostinil (Cohort 1) or from inhaled prostacyclin (Cohort 2) will be based on the percentage of subjects successfully transitioning to oral treprostinil. A successful transition is defined as a subject from Cohort 1 or 2 who is receiving oral treprostinil and no longer receiving IV/SC Remodulin or inhaled prostacyclin, respectively at Week 4 and clinically maintained on oral treprostinil treatment through Week 24. A successful initiation of oral treprostinil (Cohort 3) will be defined as a subject who has been clinically maintained on oral treprostinil through Week 24. Analysis of secondary endpoints will be descriptive in nature. Numeric endpoints for post-Baseline assessments will be compared to Baseline using Wilcoxon signed rank test, and p-values will be calculated for descriptive purposes; no formal hypothesis testing is planned.
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1 BACKGROUND AND RATIONALE

1.1 DEFINITION OF CLINICAL PROBLEM

Pulmonary arterial hypertension (PAH) is defined as an elevation in mean pulmonary arterial pressure (PAPm) greater than 25 mmHg at rest as measured by right heart catheterization (RHC) and is also associated with an increase in pulmonary vascular resistance (PVR). Elevation in PVR causes an increase in right ventricular afterload, impairing right ventricular function and ultimately leading to heart failure and death.

The typical etiologies of PAH include idiopathic (IPAH), heritable (FPAH), or associated with collagen vascular/connective tissue disease, portal hypertension, infection with the human immunodeficiency virus (HIV), history of cocaine or appetite suppressant drug use. Estimates of disease incidence have been reported between 2.4 and 7.6 cases per million individuals [Peacock 2007; Humbert 2006].

There are three major factors thought to contribute to the increased pulmonary vascular resistance seen in this disease: vasoconstriction, remodeling of the vessel wall, and thrombosis. There are a number of metabolic pathways which contribute to these changes that involve vasoactive mediators such as the vasodilators nitric oxide and prostacyclin, and the vasoconstrictor endothelin-1. These substances affect both vascular tone and remodeling leading to their use as pharmacologic targets [Farber, 2004].

PAH occurs in both adults and children. Of the etiological subgroups of PAH, congenital heart disease (CHD) and IPAH are the most common etiologies in pediatric patients [Beghetti, 2008; van Loon, 2011]. For the annual incidence and point prevalence averaged, respectively for IPAH and PAH-CHD, has been estimated at 0.7 and 4.4 (IPAH) and 2.2 and 15.6 (PAH-CHD) cases per million children [van Loon, 2011]. The characteristic pathologic processes of pulmonary vasoconstriction, endothelial dysfunction, vascular remodeling, inflammation, and thrombosis that characterize PAH in adults are also observed in children [Galie, 2009]. Although, more pulmonary vascular medial hypertrophy and a lesser amount of intimal fibrosis and formation of plexiform lesions is observed in children compared to adults [Barst, 2011]. It has also been observed that the prevalence of acute vasoreactivity is

higher in children with IPAH than adults with IPAH, suggesting that vasoconstriction may precede vascular remodeling in this subset of PAH patients [Rosenzweig, 2004; Tissot, 2009].

Clinical symptoms are similar in children and adults, and include exertional dyspnea, fatigue, chest pain and syncope. Syncope and near-syncope presents more commonly in children than adults. Additionally, children appear to tolerate increased workload on the right heart better than in adults, with better preservation of cardiac output and less frequent occurrence of right heart failure with edema [Barst, 2011]. Dyspnea is the most common symptom in older children, occasionally accompanied with chest pain [Rosenzweig, 2004].

Pediatric patients with PAH are currently diagnosed, classified, and treated in the same manner as adults. Treatment efficacy in adults is commonly measured by the change in World Health Organization (WHO) classification or exercise capacity, usually measured as the change in the six minute walk distance (6MWD). Unfortunately, the 6MWD can be difficult to reliably assess in children and may underestimate a child's exercise limitations [Ivy, 2006; Tissot, 2009; Barst, 2011]. Cardiopulmonary exercise testing (CPET) with gas exchange is a complementary non-invasive test to measure functional capacity and better reflect functional status, especially in children with a 6MWD of more than 300 meters [Ivy, 2006; Adatia, 2013; Barst, 2011].

Changes in hemodynamic parameters measured with right heart catheterization can be used to measure treatment efficacy; however, there is increased risk as general anesthesia is required to perform this procedure in the pediatric population [Carmosino, 2007]. Biomarkers, such as brain natriuretic peptide (BNP), have also been positively correlated with disease severity in children and can be used to measure treatment efficacy [Bernus, 2009].

Children with IPAH have a worse prognosis than adults, with an estimated median survival of less than one year. Children also have a shorter length of time between the onset of symptoms and diagnosis [D'Alonzo, 1991; Galie, 2009; Rosenzweig, 2004]. Overall 5-year pediatric PAH survival estimates have been reported between 64% and 81%; although one study reported survival without transplantation or atrial septostomy as 57% [Yung, 2004; van Loon, 2010; Haworth, 2009].

1.2 ORAL TREPROSTINIL BACKGROUND

Prostacyclin is an endogenous substance produced by vascular endothelium with potent vasodilating, antiplatelet aggregation, and antiproliferative properties. 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 tricyclic benzindene analogue of prostacyclin. Treprostinil is approved as the inhaled (Tyvaso®), intravenous (IV)/subcutaneous (SC) (Remodulin®) and oral (Orenitram®) formulations for the treatment of pulmonary arterial hypertension in adults.

Oral treprostinil is an innovative diolamine salt form of treprostinil formulated as an extended release osmotic tablet for oral administration, and exists in the same biologically active form in the plasma as the inhaled and parental formulations. The tablet core is coated with a semi-permeable membrane and has a laser-drilled aperture through the membrane. Upon contact with water (*e.g.*, after ingestion), the core tablet absorbs water through the semi-permeable membrane. The water dissolves the water-soluble treprostinil diolamine and the water-soluble osmotic excipients, which creates hydrostatic pressure within the membrane, eventually forcing the drug out through the tablet at a controlled rate. Oral treprostinil was recently approved in the United States under the brand name Orenitram for the treatment of pulmonary arterial hypertension WHO Group 1 in adults.

1.2.1 General Pharmacology

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 pre-contracted mesenteric arteries and inhibition of adenosine diphosphate (ADP) induced platelet aggregation in human and rat platelet rich plasma. In animals, the vasodilatory effects of treprostinil reduce right and left ventricular afterload, also 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 reverse 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.

1.2.2 General Toxicology

Treprostinil diolamine did not demonstrate any carcinogenic effects in mouse or rat carcinogenicity studies. Oral administration of treprostinil diolamine to Tg.rasH2 mice at 0, 5, 10 and 20 mg/kg/day in males and 0, 3, 7.5 and 15 mg/kg/day in females daily for 26 weeks did not significantly increase the incidence of tumors. The exposures obtained at the highest dose levels used in males and females are about 8- and 17-fold, respectively, the human exposure at the mean dose of 3.4 mg BID. Oral administration of treprostinil diolamine to Sprague Dawley rats at 0, 1, 3 and 10 mg/kg/day daily for 104 weeks did not significantly increase the incidence of tumors. The exposures obtained at the highest dose levels used in males and females are about 25- and 40-fold, respectively, the human exposure at the mean dose of 3.4 mg BID.

In vitro genotoxicity studies with high doses of treprostinil did not demonstrate any mutagenic or clastogenic effects. Treprostinil as the diolamine salt was tested *in vivo* in a rat micronucleus assay and did not induce an increased incidence of micronucleated polychromatic erythrocytes.

No adverse effect doses for fertility, fetal viability/growth, fetal development (teratogenicity), and postnatal development were determined in rats. In pregnant rabbits, external fetal and soft tissue malformations and fetal skeletal malformation occurred with the no observed adverse effect level for these adverse effects of 0.5 mg/kg/day (five times the human exposure).

1.2.3 Clinical Pharmacology

The absolute bioavailability following administration of the oral treprostinil extended release tablet is 17% compared with IV Remodulin. Maximum treprostinil concentrations occur between approximately 4 and 6 hours following administration of oral treprostinil in adults.

Following administration, oral treprostinil is widely distributed. Oral treprostinil is approximately 96% protein bound with no effect on warfarin or digoxin displacement. Pharmacokinetic area under the curve (AUC) data; indicate that Day 1 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 calorie meal, has been observed to increase absorption and prolong exposure, contributing to the desired pharmacokinetic profile. The relative bioavailability of treprostinil following oral administration of a 1 mg extended release tablet was not significantly altered by meal types ranging from 250 to 500 calories in healthy adult volunteers.

Treprostinil is primarily metabolized by cytochrome (CYP) 2C8 and to a lesser extent by CYP2C9. It is unknown if the metabolism of oral treprostinil will be altered in pediatric patients. A study evaluating the metabolism of paclitaxel by CYP2C8 using pediatric and adult liver microsomes found no age-related differences in metabolism [Blanco, 2000]; however, CYP2C9 activity appears to be increased in children. Clearance is approximately twice that of adult values for several drugs predominately metabolized by CYP2C9, including warfarin, phenytoin, and celecoxib [Anderson, 2009]. Co-administration of oral treprostinil with a strong CYP2C8 inhibitor (*e.g*., gemfibrozil) has been demonstrated to result in significant elevation of treprostinil plasma concentrations.

In a study conducted in healthy volunteers using [^{14}C] treprostinil, 78.6% and 13.4% of the subcutaneous dose was recovered in the urine and feces, respectively, over 10 days. Only 4% was excreted as unchanged treprostinil in the urine. Five metabolites were detected in the urine, ranging from 10.2% to 15.5% and representing 64.4% of the dose administered. Metabolites of treprostinil were tested for pharmacologic activity and found to be much less hemodynamically active than treprostinil itself. Specifically, metabolite M388 was 100- to 1,000-fold less active than treprostinil, metabolites M392 and M566 were 1,000-fold less active than treprostinil, and metabolite M334 was at least 10,000-fold less active than treprostinil (i.e., did not affect blood pressure or heart rate at the highest dose tested). Metabolites M348 and M374 likewise had little cardiovascular activity, having some

0.01-0.05% the activity of parent drug. It is concluded that the metabolites contributed very little to pharmacologic activity in this model.

Initial clinical studies used a twice a day dosing regimen; however, a three times a day dosing (TID) regimen has been evaluated and a reduction in the peak-to-trough fluctuations observed. A TID regimen more closely resembles a parental infusion to facilitate the achievement of higher doses with greater clinical effect on the signs and symptoms of PAH, and reduces the occurrence of prostacyclin-related adverse events previously seen with the twice daily regimen. Successful transition of stable adult PAH subjects from parenteral treprostinil (IV or subcutaneous [SC] infusion) to a TID regimen with oral treprostinil without a significant decline in exercise capacity or worsening functional classification has been demonstrated in a recent clinical trial [White, 2014].

1.2.4 Clinical Trials Experience

Oral treprostinil has been administered to over 1,800 subjects in phase I-III trials. Doses of up to 3 mg BID have been administered to healthy volunteers and subjects with PAH have received up to 28 mg TID in phase III and open-label studies. As reported as of February 2014, the average exposure has been approximately two years and the longest exposure reported as almost six years.

Oral treprostinil has been evaluated in studies in subjects with PAH as monotherapy and in combination with endothelin receptor antagonist (ERA) and phosphodiesterase type 5 inhibitor (PDE-5i) therapies.

In a 12-week, randomized (2:1 oral treprostinil to placebo), double-blind, placebo-controlled, international study in subjects with WHO Group 1 PAH not currently receiving PAH therapy, subjects receiving oral treprostinil improved their median 6MWD at Week 12 by approximately +23 meters (Hodges-Lehmann estimate; p=0.013, non-parametric analysis of covariance in accordance with the pre-specified statistical analysis plan in the primary analysis population; n=228) as compared to subjects receiving placebo. The within group median change from baseline was +25 meters for oral treprostinil and -5 meters for placebo at

Week 12 (n=228). Mean dose (±SD) in the oral treprostinil group was 2.3 ±1.3, 3.2 ±1.9, and 3.4 ±1.9 mg BID at Weeks 4, 8, and 12, respectively.

The study enrolled 349 subjects (overall analysis population) who were not receiving any PAH medication. Subjects were in WHO functional class II (~33%) and class III (~66%) with either idiopathic or heritable PAH (~75%), collagen vascular disease associated PAH (~19%), or PAH associated with HIV (1%) or congenital heart defect (5%) or other conditions (~6%). The mean baseline 6MWD was approximately 330 meters.

Subjects were administered oral treprostinil or placebo twice daily, with the doses titrated to effect up to a maximum of 12 mg BID based on clinical response and study drug tolerability. At the beginning of the study, subjects were dosed with only the 1 mg tablets, with 0.5 and 0.25 mg tablets introduced at sequentially later dates during the study. The primary analysis population consisted of the 228 subjects who had access to the 0.25 mg tablet at the time of randomization. Discontinuations occurred in 17% of subjects receiving oral treprostinil compared to 14% of subjects on placebo in this population.

Two 16-week, randomized, double-blind, placebo-controlled, international efficacy and safety studies of oral treprostinil in subjects with WHO Group 1 PAH already receiving treatment with an ERA, PDE-5i or a combination of both have been conducted. The results did not demonstrate a benefit in exercise testing with median 6MWD at Week 16 (11 meters [Hodges-Lehmann estimate; p=0.072] and 10 meters [Hodges-Lehmann estimate; p=0.089], respectively). Subjects were in WHO functional classification II (~23%) and III (~77%) with either idiopathic or heritable PAH (~66%), collagen vascular disease associated PAH (~29%), or PAH associated with HIV (1%) or congenital heart defect (4%). The mean baseline 6MWD was approximately 340 meters. Approximately 40% of enrolled subjects were receiving both an ERA and a PDE-5i.

Over 824 subjects have received oral treprostinil in a long-term, uncontrolled, open-label ongoing extension study. About 70% of subjects continued treatment with oral treprostinil for at least a year. The mean dose was 4.2 mg BID at one year. The dose of oral treprostinil continued to increase over time with doses (mean ± SD) of 3.6 ±2.7, 4.1 ±3.1, and 5 ±3.7 mg

BID at 6 (n=649), 12 (n=433), and 24 months (n=238), respectively. In the 522 subjects that completed the 12-month efficacy assessment, their mean 6MWD improved by 24 meters compared to baseline (30 meters in subjects not on another PAH therapy and 20 meters when oral treprostinil was used in combination with an ERA and/or a PDE-5i). Of the subjects that remained in the study, overall survival was 92%, 87%, and 82% at the end of 1, 2, and 3-years, respectively, with progression-free survival (progression defined as death, discontinuation or addition of a PAH therapy) of 74%, 61%, and 47%. Reasons for discontinuation from the study included adverse event (16%), progression of disease (15%), death (13%), and withdrawn consent (7%).

The most frequent adverse events (AEs) associated with oral treprostinil that occurred more frequently than placebo in clinical trials were related to systemic effects that are characteristic of prostacyclin (*e.g.*, headache, diarrhea, nausea, flushing, pain in jaw, pain in extremity).

A comprehensive description of oral treprostinil, including the pharmacology, toxicology, and clinical studies completed to date may be found in the Orenitram Package Insert and current version of the Investigators' Brochure.

1.3 RATIONALE FOR DEVELOPMENT OF STUDY DRUG IN DISEASE/CONDITION

Parenteral prostacyclins are considered by many providers as the "gold standard" treatment for PAH. Currently, the complexity and risks associated with approved prostanoid therapy including line sepsis, thromboembolism, and rebound hypertensive crisis limit its utility in clinical practice, particularly in children [Melnick, 2010]. Because of the risks and limitations of continuous parenteral infusion, an alternative route of administration would be desirable for adults as well as children.

Oral treprostinil is a prostacyclin analogue, a class of medication that has long played a prominent role in the treatment of PAH [Badesch, 2004]. Prostacyclin, an endogenous compound produced by the vascular endothelium, has several activities that are relevant to the treatment of pulmonary arterial hypertension. The similarity between adults and children with PAH in underlying pathobiological mechanisms supports the extrapolation that medicinal

products that are effective in adults would also be effective in children. In addition to the data in adult patients establishing the safety and efficacy and supporting the regulatory approval of parenteral prostacyclin and prostacyclin analogue products, it has been reported that the use of IV epoprostenol in children is associated with clinical benefit and improved survival [Barst, 1999; Yung, 2004]. In a recent observational study evaluating the efficacy and tolerability of SC treprostinil for refractory pediatric pulmonary hypertension, eight children aged from 15 months to 10 years old received SC treprostinil therapy at doses ranging from 37-60 ng/kg/min. Of the eight children treated, seven showed improvement in functional classification, hemodynamic, and/or 6MWD ($p<0.05$), suggesting treprostinil is effective in children with pulmonary hypertension [Levy, 2011]. Additionally, a study in 13 children aged 3-17 years with PAH suggested that IV treprostinil is a therapeutic alternative to IV epoprostenol, with fewer side effects [Ivy, 2007]. Successful transitions from IV to oral or inhaled therapies (PDE-5i, ERA, calcium channel blockers, inhaled iloprost) have been previously demonstrated in studies in children aged six years or greater [Ivy, 2004; Melnick, 2010]. A retrospective study of 77 pediatric PAH patients receiving epoprostenol (n=37), treprostinil (n=20), or were transitioned from epoprostenol to treprostinil (n=20), reported a 5-year transplant-free survival of 70% (95% confidence interval, 56%-80%). Hemodynamic changes over time on treprostinil were similar to epoprostenol. There was a significant improvement in the pulmonary-to-systemic vascular resistance ratio with treprostinil after 2 years of therapy and a trend toward improvement on epoprostenol after 1 to 2 years of therapy; although, these changes were not sustained over the 4 year follow-up period [Siehr, 2013].

Given the established beneficial effects of prostanoid therapy in PAH and the limitations of existing prostanoid medications, oral treprostinil may provide therapeutic benefit to pediatric patients with PAH who are old enough to safely take the medication.

1.4 CLINICAL HYPOTHESIS

This study aims to test the safety and tolerability of oral treprostinil in three cohorts of pediatric subjects aged 7 to 17 years: transitioning from IV/SC Remodulin, transitioning from inhaled prostacyclin, and as add-on to current PAH therapy in de novo prostacyclin subjects.

The hypothesis of this study is that stable PAH pediatric subjects can be safely be transitioned from IV/SC Remodulin to oral treprostinil therapy while maintaining the clinical benefit of the infused therapy. A recent study in stable, carefully-selected PAH adult subjects receiving IV/SC Remodulin demonstrated that subjects can be safely transitioned to oral treprostinil three times daily (TID) dosing under close medical observation without a significant decline in exercise capacity or worsening functional classification [White, 2014]. After analysis of interim pharmacokinetic data from this study, it was determined that a four times daily (QID) dosing regimen in select pediatric subjects may achieve a better pharmacokinetic profile than a TID regimen, potentially providing a clinical benefit. Additionally, we hypothesize that initiation of oral treprostinil in pediatric subjects following transition from inhaled prostacyclin or added to current PAH therapies in de novo prostacyclin subjects will result in clinical improvement compared to Baseline.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

To assess the safety and tolerability of oral treprostinil extended release tablets in three cohorts of pediatric subjects with PAH aged 7 to 17 years:

- Cohort 1: Subjects transitioning from IV/SC Remodulin
- Cohort 2: Subjects transitioning from inhaled prostacyclin
- Cohort 3: As add-on to current PAH therapy in de novo prostacyclin subjects

2.2 SECONDARY OBJECTIVES

1. To assess the effect of oral treprostinil on the following (assessed in all cohorts):
    - CPET with progressive cycle ergometry
    - Symptoms of PAH
    - Panama and WHO functional classification
    - 6MWD with oximetry and heart rate (HR) recovery monitoring
    - Borg dyspnea score
    - Quality of life (QOL) assessed via the Pediatric Quality of Life Inventory (PedsQL) questionnaire

- Plasma N-terminal pro-B-type natriuretic peptide (NT-Pro BNP)
- Cardiac magnetic resonance imaging (cMRI)

2. To describe treprostinil pharmacokinetics (PK) in pediatric subjects with PAH aged 7 to 17 years.

3 EXPERIMENTAL PLAN

3.1 STUDY DESIGN

This is a multi-center, open-label, safety and tolerability study of oral treprostinil (study drug) administered TID or QID, at the discretion of the Investigator, with food in pediatric PAH subjects aged 7 to 17 years of age (1) transitioning from continuous IV/SC Remodulin; (2) transitioning from inhaled prostacyclin; or (3) as add-on to current PAH therapies in de novo prostacyclin subjects. Eligible subjects will be assigned to a cohort based upon their background therapy.

Up to seven study visits will occur during the 24-week study at the following time points; Screening, Baseline, Week 0 (Cohort 1 only; inpatient hospital stay Days 1-5), Week 3, Week 6, Week 12, and Week 24.

Cohort 1 Subjects:
Following completion of Baseline assessments, including an 8-hour PK assessment while receiving IV/SC Remodulin within seven days prior to the first dose of oral treprostinil, subjects in Cohort 1 will undergo an inpatient hospital stay lasting approximately five days to transition from IV/SC Remodulin to oral treprostinil. The target transition goal is five days and for the subject to be completely transitioned off IV/SC Remodulin prior to discharge from the hospital. Subjects will be discharged from the hospital after they have transitioned off IV/SC Remodulin, reached their target oral treprostinil dose, or as the Investigator deems appropriate. If necessary or if appropriate per Investigator discretion, subjects can prolong or complete the transition in an outpatient setting for a total transition time of up to four weeks.

The maximum time to titrate off IV/SC Remodulin is four weeks from the start of the transition; if the subject is not fully transitioned by Week 4, they will be removed from the

study. If the subject is in the hospital during one of the scheduled study visits, the assessments for that visit will be conducted as scheduled during the defined visit window.

Cohort 2 and 3 Subjects:

Following completion of Baseline assessments, the first dose of 0.125 mg oral treprostinil should be taken at the study site. Dosing of oral treprostinil will be initiated at 0.125 mg TID or QID at the discretion of the investigator, with food. Dosing will take place approximately every 6 to 8 hours for TID dosing, or approximately every 4 to 6 hours for QID dosing, with adjustments permitted based on the subject's lifestyle and schedule. Dose changes should be conducted under appropriate medical supervision in consultation with the study site.

Dose Optimization/Evaluation Phase (All Cohorts):

Week 3, Week 6, and Week 12: Subjects will return to clinic for the following assessments: vital signs, six-minute walk test (6MWT)/Borg dyspnea score, Panama and WHO functional classification, symptoms of PAH, and safety assessments. At each visit, females of childbearing potential will undergo a urine pregnancy test. At Week 12, QOL (as measured by PedsQL) and clinical laboratory assessments, including NT-pro-BNP, will occur.

Week 24 (or premature termination): Subjects will return to the clinic for the following assessments: vital signs, physical examination, 6MWT/Borg dyspnea score, CPET, Panama and WHO functional classification, symptoms of PAH, QOL assessment, NT-Pro BNP, cMRI, clinical laboratory assessments, electrocardiogram (ECG), and safety assessments. Females of child bearing potential will undergo a urine pregnancy test. In addition all subjects will undergo an 8-hour PK assessment.

Once the first five subjects have enrolled in Cohort 1 and transitioned from IV/SC Remodulin, the safety data will be reviewed by a Data Safety Monitoring Board (DSMB). The IV/SC Remodulin dose will be between 25-75 ng/kg/min, inclusive, for the first five subjects enrolled in the cohort. The dose range may be expanded to 25-125 ng/kg/min, inclusive, for the remaining subjects following the safety review.

Additionally, if two or more of the first five subjects within any cohort meet the pre-specified stopping criteria (see Section 5.4) the data from that cohort will be reviewed by the DSMB

prior to enrolling additional subjects into that cohort. If any of these events happen after the first four weeks of the study, it is not required that a subject be removed from the study. The Investigator will determine whether it is safe for a subject to remain in the study.

3.2 OVERALL SCHEDULE OF TIMES AND EVENTS

No study-related procedures will be performed before a subject and/or their legal guardian has provided written informed consent and assent, as per institutional requirements. All study-related events and activities including specific instructions, procedures, concomitant medications, and descriptions of AEs will be recorded in the appropriate source documents and electronic case report forms (eCRFs).

Table 3-1 Cohort 1 Schedule of Times and Events

Study Visit/Week	Screening[a]	Baseline[a]	Treatment[c]					
			Transition Phase			Dose Optimization/Evaluation		
			Week 0[a]	Week 3[b]	Week 4[n]	Week 6[b]	Week 12[b]	Week 24[b]/ Premature Termination[c]
Study Day	**-28 to -1**	**0/1**	**2–5 (daily)**	**22**	**29**	**43**	**85**	**169**
Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
Demographics	X							
PAH History	X							
Medical History	X							
Physical Examination	X							X
PedsQL Questionnaire[d]		X					X	X
Vital Signs[e]	X	X	X	X		X	X	X
Clinical Laboratory Parameters	X	X					X	X
NT-pro-BNP		X[f]					X[f]	X[f]
Urine Pregnancy Test[g]	X	X		X		X	X	X
12-lead ECG		X						X
Cardiac MRI[h]		X						X
Panama and WHO Functional Classification	X	X		X		X	X	X
PAH Symptoms		X	X	X		X	X	X
6MWT/Borg Dyspnea Score	X[i]	X[i]	X[j]	X[k]		X[k]	X[k]	X[k]
CPET		X[l]						X[l]
Pharmacokinetic Evaluation		X[m]						X[m]
Hospital Stay		X	X					
IV/SC Remodulin Weaning[n]		X	-------	-------	X			
Administration of Oral Treprostinil		X	-------	-------	-------	-------	-------	------

Study Visit/Week	Screening[a]	Baseline[a]	Treatment[c]					
			Transition Phase			Dose Optimization/Evaluation		
			Week 0[a]	Week 3[b]	Week 4[n]	Week 6[b]	Week 12[b]	Week 24[b]/ Premature Termination[c]
Study Day	**-28 to -1**	**0/1**	**2–5 (daily)**	**22**	**29**	**43**	**85**	**169**
Dosing Instructions / Dosing Diary		X		X		X	X	
Drug Accountability / Compliance				X		X	X	X
Telephone Contact[o]			X-------		-------	-------	-------	------X
Adverse Events[p]	X-------	-------	---X[q]---	--------	-------	-------	-------	------X
Concomitant Medications	X-------	-------	-------	--------	-------	-------	-------	------X
Pre-Baseline Review Form[r]	-------X							

[a] The Screening phase can begin up to 28 days prior to Baseline. Baseline assessments can be conducted over five days (120 hours) prior to the first dose of oral treprostinil, to allow for scheduling of all activities. Screening and Baseline visits may be combined if all assessments are completed and entry criteria are satisfied within five days (120 hours) prior to first dose of oral treprostinil. Baseline PK assessments for subjects enrolled in Cohort 1 can be performed up to seven days prior to beginning oral treprostinil. The subject will begin transitioning from IV/SC Remodulin to oral treprostinil in the hospital (Week 0).

[b] The window for Week 3, 6, 12, and 24 visits is ± five days.

[c] The Week 24/Premature Termination visit can occur over five days (120 hours) to allow for scheduling of assessments on separate days; however, no oral treprostinil dose adjustments are allowed from five days prior to the Week 24 study visit until all Week 24/Premature Termination procedures have been completed, unless required to protect subject safety. If the subject discontinues the study before Week 24, then the Premature Termination visit should be conducted. All assessments should be conducted prior to discontinuation of oral treprostinil or as close as possible to the last dose of study drug.

[d] PedsQL questionnaires must be completed based upon the subject's age group and in accordance with the questionnaire administration guidelines. Must be completed as the first assessment at Baseline (or as part of the Screening visit assessment [after informed consent is obtained] if the Screening and Baseline visits are combined), Week 12 and Week 24 /Premature Termination, before the respondents complete any other health data forms, and before they see their physician/healthcare provider or have other assessments performed.

[e] Vital signs must be collected after five minutes of rest (sitting); no other measurements or procedures should be performed during this five-minute period. All vital signs will be collected prior to or after at least 30 minutes following the 6MWT.

[f] Blood for NT-pro-BNP assessment must be drawn prior to conducting the 6MWT or CPET and will occur prior to the first dose of oral treprostinil at Baseline (or as part of the Screening visit assessment if the Screening and Baseline visits are combined).

[g] Urine pregnancy test will be conducted for all females of childbearing potential. If Screening and Baseline assessments are combined, a pregnancy test only needs to be conducted once.

[h] cMRI is optional for children younger than 10 years of age. Must be performed prior to 6MWT and CPET if done on the same day. If subject requires anti-anxiety medication (no general anesthesia) during the cMRI (without contrast), then the cMRI should be performed on a separate day from the CPET and 6MWT.

[i] 6MWT is only required at Screening if the subject has not previously undergone a 6MWT/Borg dyspnea score at the study site. In that case, a practice test must be conducted and must precede the Baseline 6MWT by at least one day. The 6MWT at Baseline must be conducted prior to the first dose of oral treprostinil. Screening (if applicable) and Baseline 6MWTs will also include oximetry and HR recovery monitoring.

[j] 6MWT will occur daily during the inpatient hospital stay and should occur within 2-6 hours of the subject's last dose (i.e., most recent dose) of oral treprostinil. This will include oximetry and HR recovery monitoring.

[k] 6MWT should occur within 2-6 hours of the subject's last dose (i.e., most recent dose) of oral treprostinil and should be performed at least two hours before the CPET when they are performed at the same day. Includes oximetry and HR recovery monitoring.

[l] CPET should be performed a minimum of two hours after the 6MWT. At Week 24, the CPET should be performed 2-6 hours after the morning dose of oral treprostinil. It may be waived for subjects less than 130 cm in height, based on equipment available at the center.

[m] Baseline PK assessments can be performed up to seven days prior to beginning oral treprostinil. Administration of the oral treprostinil dose on the day of Week 24 PK sampling should occur approximately 8 hours after the prior evening's last oral treprostinil dose for subjects using the morning dose for the PK assessment. When using the midday dose for the PK assessment, the midday dose of oral treprostinil should occur approximately 4 to 6 hours after that day's morning dose. No oral treprostinil dose changes are allowed within five days of the Week 24 PK sampling, unless required to protect subject safety. See Section 3.3.3 and Section 15.5.

[n] The maximum time to titrate off IV/SC Remodulin is four weeks from the start of the transition; if the subject is not fully transitioned by Week 4, they will be removed from the study. Subjects do not need to return to clinic for a visit at Week 4.

[o] Daily telephone contact (excluding weekends and inpatient hospital stay) is required for the first two weeks of the study. Weekly telephone contact is required from the Week 3 visit until the Week 12 visit and then at least every other week until the Week 24 visit. Subjects may be contacted via email in lieu of a telephone call. A copy of the emails and/or telephone contact sheets must be documented in the subject's source documentation. Email should not replace direct follow-up by phone or in clinic for clinical significant AEs or other emergent issues.

[p] All AEs will be documented from the time of informed consent until the time screen failure is documented, or until the subject is either discontinued from the study or all Week 24 study assessments have been completed and 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 30 days if the AE extends beyond the final study visit.

[q] Detailed prostacyclin-related AE collection will occur during the inpatient transition phase.

[r] A pre-baseline review form must be completed and submitted for Sponsor approval after all screening assessments have been conducted for permission to move forward with the Baseline visit assessments.

Table 3-2 Cohort 2 and Cohort 3 Schedule of Times and Events

Study Visit/Week	Screening[a]	Baseline[a]	Treatment[c]			
			Week 3[b]	Week 6[b]	Week 12[b]	Week 24[b] / Premature Termination[c]
Study Day	**-28 to -1**	**0/1**	**22**	**43**	**85**	**169**
Informed Consent	X					
Inclusion/Exclusion Criteria	X	X				
Demographics	X					
PAH History	X					
Medical History	X					
Physical Examination	X					X
Clinical Laboratory Parameters	X	X			X	X
Urine Pregnancy Test[d]	X	X	X	X	X	X
PedsQL Questionnaire[e]		X			X	X
Vital Signs[f]	X	X	X	X	X	X
12-lead ECG		X				X
Cardiac MRI[g]		X				X
PAH Symptoms		X	X	X	X	X
Panama and WHO Functional Classification	X	X	X	X	X	X
NT-pro-BNP		X[h]			X	X[h]
6MWT/Borg Dyspnea Score	X[i]	X[i]	X[j]	X[j]	X[j]	X[j]
CPET		X[k]				X[k]
Pharmacokinetic evaluation[l]						X
Administration of oral treprostinil		X	--------	--------	-------	------
Dosing Instructions / Dosing Diary		X	X	X	X	
Drug Accountability / Compliance			X	X	X	
Telephone Contact[m]		X----	-------	--------	-------	------X
Adverse Events[n]	X-------	-------	--------	--------	-------	------X

Study Visit/Week	Screening[a]	Baseline[a]	Treatment[c]			
			Week 3[b]	Week 6[b]	Week 12[b]	Week 24[b] / Premature Termination[c]
Study Day	**-28 to -1**	**0/1**	**22**	**43**	**85**	**169**
Concomitant Medications	X-------	-------	--------	--------	-------	------X
Pre-Baseline Review Form[o]	-------X					

[a] The Screening phase can begin up to 28 days prior to Baseline. Baseline assessments can be conducted over five days (120 hours) prior to the first dose of oral treprostinil, to allow for scheduling of all activities. Screening and Baseline visits may be combined if all assessments are completed and entry criteria are satisfied within five days (120 hours) prior to first dose of oral treprostinil.

[b] The window for Week 3, 6, 12 and 24 visits is ± five days.

[c] The Week 24/Premature Termination visit can occur over five days (120 hours) to allow for scheduling of assessments on separate days; however, no oral treprostinil dose adjustments are allowed from five days prior to the Week 24 study visit until all Week 24/Premature Termination procedures have been completed, unless required to protect subject safety. If the subject discontinues the study before Week 24, then the Premature Termination visit should be conducted. All assessments should be conducted prior to discontinuation of oral treprostinil or as close as possible to the last dose of study drug.

[d] Urine pregnancy test will be conducted for all females of childbearing potential. If Screening and Baseline assessments are combined, a pregnancy test only needs to be conducted once.

[e] PedsQL questionnaires must be completed based upon the subject's age group and in accordance with the questionnaire administration guidelines. Must be completed as the first assessment at Baseline (or as part of the Screening visit assessment [after informed consent is obtained] if the Screening and Baseline visits are combined), Week 12 and Week 24/Premature Termination, before the respondents complete any other health data forms, and before they see their physician/healthcare provider or have other assessments performed.

[f] Vital signs must be collected after five minutes of rest (sitting); no other measurements or procedures should be performed during this five-minute period. All vital signs will be collected prior to or after at least 30 minutes following the 6MWT.

[g] cMRI is optional for children younger than 10 years of age. Must be performed prior to 6MWT and CPET if done on the same day. If subject requires anti-anxiety medication (no general anesthesia) during the cMRI (without contrast), then the cMRI should be performed on a separate day from the CPET and 6MWT.

[h] Blood for NT-pro-BNP assessment must be drawn prior to conducting the 6MWT or CPET and will occur prior to the first dose of oral treprostinil at Baseline (or as part of the Screening visit assessment if the Screening and Baseline visits are combined).

[i] 6MWT is only required at Screening if the subject has not previously undergone a 6MWT/Borg dyspnea score at the study site. In that case, a practice test must be conducted and must precede the Baseline 6MWT by at least one day. The 6MWT at Baseline must be conducted prior to the first dose of oral treprostinil. Screening (if applicable) and Baseline 6MWTs will also include oximetry and HR recovery monitoring.

[j] 6MWT should occur within 2-6 hours of the subject's last dose (i.e., most recent dose) of oral treprostinil and should be performed at least two hours before the CPET when they are performed at the same day. This will include oximetry and HR recovery monitoring.

[k] CPET should be performed a minimum of two hours after the 6MWT. At Week 24, the CPET should be performed 2-6 hours after the morning dose of oral treprostinil. It may be waived for subjects less than 130 cm in height, based on equipment available at the center.

[l] Administration of the oral treprostinil dose on the day of Week 24 PK sampling should occur approximately 8 hours after the prior evening's last oral treprostinil dose for subjects using the morning dose for the PK assessment. When using the midday dose for the PK assessment, the midday dose of oral treprostinil should occur approximately 4 to 6 hours after that day's morning dose. No oral treprostinil dose changes are allowed within five days of the Week 24 PK sampling, unless required to protect subject safety. See Section 3.3.3 and Section 15.5.

[m] Daily telephone contact (excluding weekends) is required for the first two weeks of the study. Weekly telephone contact is required from the Week 3 visit until the Week 12 visit and then at least every other week until the Week 24 visit. Subjects may be contacted via email in lieu of a telephone call. A copy of the emails and/or telephone contact sheets must be documented in the subject's source documentation. Email should not replace direct follow-up by phone or in clinic for clinical significant AEs or other emergent issues.

[n] All AEs will be documented from the time of informed consent until the time screen failure is documented, or until the subject is either discontinued from the study or all Week 24 study assessments have been completed and 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 30 days if the AE extends beyond the final study visit.

[o] A pre-baseline review form must be completed and submitted for Sponsor approval after all screening assessments have been conducted for permission to move forward with the Baseline visit assessments.

3.3 CLINICAL ASSESSMENTS

3.3.1 Efficacy

3.3.1.1 Cardiopulmonary Exercise Testing (CPET)

Exercise testing will be performed with progressive cycle ergometry and ventilatory expired gas analysis obtained using a metabolic cart at Baseline and Week 24/Premature Termination. The CPET may be waived in subjects less than 130 cm in height based on equipment available at the center. Cardiopulmonary exercise testing entails measurements of oxygen uptake (VO_2), carbon dioxide output (VCO_2), minute ventilation (VE) and other variables, in addition to a 12-lead ECG, blood pressure (BP) monitoring, and pulse oximetry. Testing should be performed a minimum of two hours after the 6MWT when they occur on the same visit, and should be conducted 2-6 hours after the morning dose of oral treprostinil (study drug) at the Week 24 visit.

Resting measurements will be made for 1-3 minutes; followed by one minute unloaded (no tension/resistance) cycling as a warm-up period. The workload will then be increased at a rate designed to allow reaching maximum work capacity in 8-12 minutes. Workload will be increased in a continuous (ramp) fashion, with 5 Watt/minute for subjects <40 kg, 10Watt/min for subjects 40 to <70 kg, and 15 Watt/min for subjects ≥70 kg. Subjects will be instructed to maintain a pedaling cadence between 50-60 revolutions per minute (RPM). Maximal effort will be defined as the attainment of a Respiratory Quotient (RQ) equal to 1.10 or greater. Subjects will be encouraged to put forth a maximal effort on CPET. Tests will be terminated according to published guidelines and institutional standards.

- Metabolic data will be continuously collected and recorded in the subject's source documentation during baseline, warm up, exercise, and the first two minutes of recovery. Breath by breath data should be averaged in 20-second intervals. Blood pressure should be recorded every 2-3 minutes with additional measurements as needed. Oxygen saturation should be measured continuously. Resting values will be selected from the baseline data. Peak values will be selected from the last portion of the exercise. The VE/VCO_2 slope will be measured to the respiratory compensation point.

- The raw exercise data will be sent to a central site and reviewed by a centralized specialist to ensure consistency and accuracy of test performance. The centralized specialist may communicate with the site and establish study specific analysis settings for assessments performed for purposes of this protocol.

3.3.1.2 Six-Minute Walk Test

The intent of the 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 as outlined in Appendix 15.1. The subject should rest (seated) for at least five minutes prior to the start of each 6MWT. The start time of the pre-walk, and five minute rest period should be clearly documented in the subject's medical records.

A 6MWT will only be required at Screening if the subject has not previously undergone a 6MWT at the study site and will serve as a practice test. If conducted, it must be separated by at least one day from the 6MWT at Baseline. Given that the 6MWT needs to be performed during inpatient hospitalization (Cohort 1 subjects only) and the subsequent study visits, it is permissible to conduct the 6MWT at different locations, if needed, during this study.

Oxygen saturation and HR will be measured at rest prior to the 6MWT and monitored continuously during the walk. Oxygen saturation may be measured by fingertip or forehead monitor. Recovery monitoring (HR and oxygen saturation) will be performed and documented at minute 0 (immediately upon stopping the 6MWT), minute 1, minute 2 and minute 3 post-walk. Recovery monitoring must continue until the HR is within 10 beats of resting values and the oxygen saturation is within 2% of resting values or until at least 20 minutes of recovery monitoring has been performed and the Investigator considers the subject to be clinically stable.

3.3.1.2.1 Baseline Six-Minute Walk Test

The 6MWT performed at Baseline must be conducted prior to the first dose of oral treprostinil. If a practice 6MWT is conducted at Screening, the Baseline 6MWT must be conducted at least one day apart. For the purposes of the 6MWT, if the subject was assessed

at Baseline using oxygen therapy, then all 6MWTs during the 24-week study should be conducted with the same oxygen flow rate and mode of administration. The 6MWT should be conducted at least two hours prior to conducting the CPET.

3.3.1.2.2 Treatment Six-Minute Walk Tests

The 6MWTs will be conducted during each day of the inpatient hospital stay (Cohort 1 subjects only) and all subsequent study visits, and should occur within 2-6 hours of the subject's last dose (i.e., most recent dose) of oral treprostinil. Subjects receiving supplemental oxygen during the Baseline 6MWT must continue to receive the same flow rate and mode of oxygen therapy at all subsequent 6MWT assessments. The 6MWT should be performed at least two hours prior the CPET at Week 24/Premature Termination.

3.3.1.3 Borg Dyspnea

The Borg dyspnea score will be assessed prior to and following the completion of each 6MWT. The Borg dyspnea score is a 10-point scale rating the maximum level of dyspnea experienced during the 6MWT (Section 15.1). Scores range from 0 (for the best condition) to 10 (for the worst condition).

3.3.1.4 PAH Symptoms

PAH symptoms (fatigue, dyspnea, edema, dizziness, syncope, chest pain, orthopnea) will be assessed at the Baseline visit prior to the initiation of oral treprostinil dosing and at all subsequent visits, including each day of the inpatient hospital stay (Cohort 1 subjects only). Scores range from 0 (for the best condition) to 3 (for the worst condition).

3.3.1.5 Functional Classification

Subject clinical status will be assessed at Screening, Baseline, and all subsequent study visits. Functional classification will be recorded according to the Panama functional classifications for children with pulmonary hypertension and the WHO functional classification. Functional classification scales are provided in Section 15.2.

3.3.1.6 N-terminal pro-BNP

Plasma N-terminal pro-BNP concentration is a useful biomarker for PAH as it is associated with changes in right heart morphology and function [Fijalkowska, 2006]. NT pro-BNP

sample collection will occur at Baseline (or as part of the Screening visit assessment if the Screening and Baseline visits are combined) prior to starting oral treprostinil and repeated at Week 12 and Week 24/Premature Termination. Blood for NT-pro-BNP assessment must be drawn prior to conducting the 6MWT or CPET.

3.3.1.7 Pediatric Quality of Life Inventory (PedsQL™)

Health-related quality of life will be assessed via the 23-item PedsQL questionnaire at Baseline (or as part of the Screening visit assessment if the Screening and Baseline visits are combined), Week 12, and Week 24/Premature Termination. The appropriate questionnaire must be administered based upon the subject's age group and in accordance with the questionnaire administration guidelines. The PedsQL must be completed as the first assessment (after informed consent is obtained) before the respondents complete any other health data forms, and before they see their physician/healthcare provider or have other assessments performed. An example of the PedsQL is provided in Section 15.3.

3.3.2 Safety

During this study, treatment emergent changes in physical findings, vital signs, clinical laboratory parameters, and the development of AEs will be the primary assessments of safety.

3.3.2.1 Medical History and Physical Examinations

A complete medical history, demographics, PAH history, and physical examination will be conducted at Screening. If any changes to the medical history occur between the Screening and Baseline visit, those should be recorded. Significant past or present illnesses, current prescription or nonprescription medications (including vitamins and herbal products), and history of medication allergies should be recorded. Any significant changes to the subject's medical condition, physical examination, and concomitant medications must be documented throughout the course of the study.

A complete physical examination will be conducted by a physician at Screening and at Week 24/Premature Termination. All treatment emergent clinically significant findings during the study will be reported as AEs.

3.3.2.2 Vital Signs

Vital signs will be assessed during all study visits, including every day of the inpatient hospital stay (Cohort 1 subjects only). Vital signs measured will include blood pressure (BP, systolic and diastolic), HR, respiratory rate (RR), temperature (°C), and weight. Vital signs must be assessed following at least five minutes of rest (sitting) to ensure accurate measurement. No other measurements or procedures should be performed during this five-minute period. Vital signs will be collected prior to or after at least 30 minutes following the 6MWT. Vital signs should also be assessed in the case of abnormal clinical signs and symptoms. Height will be recorded at Screening.

3.3.2.3 12-Lead ECG

A 12-lead ECG will be recorded after at least five minutes rest in the semi-recumbent position at Baseline and repeated at Week 24/Premature Termination. Recordings should include lead II as a rhythm strip and contain at least five QRS complexes. The ECG parameters (after at least five minutes rest) include HR, PR interval, QT interval, QRS duration, and any clinically significant abnormalities.

3.3.2.4 Clinical Laboratory Assessments

The results of all clinical laboratory tests conducted at Screening and Baseline must be assessed by the Investigator to determine each subject's eligibility to participate in the study. Clinical laboratory results outside the normal reference range must be assessed and documented by the Investigator as to clinical significance. Clinically significant refers to a laboratory value that is unusual with respect to the subject's medical history or current health status.

Clinically significant abnormal laboratory test values will be treated and/or followed-up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator. When appropriate, medical tests and examinations will be performed to document resolution of event(s).

3.3.2.4.1 Clinical Chemistry and Hematology

Blood and urine specimens for the measurement and evaluation of clinical chemistry and hematology will be collected at the Screening and Baseline visits prior to administration of oral treprostinil and repeated at the Week 12 and Week 24/Premature Termination to assess for study treatment-emergent changes in clinical chemistry and hematological laboratory parameters. Values for the following parameters will be obtained:

Electrolyte Panel

- Sodium
- Potassium
- Bicarbonate
- Chloride

Chemistry Panel

- Total bilirubin
- Alkaline phosphatase
- Alanine aminotransferase
- Aspartate aminotransferase
- Urea nitrogen
- Creatinine
- Calcium
- Albumin

Hematology Panel

- Hemoglobin
- Hematocrit
- Red blood cell count
- Red blood cell morphology
- White blood cell count
- Platelet count

3.3.2.4.2 Pregnancy Testing

Females of childbearing potential include any female who has experienced menarche. Urine pregnancy tests (for all females of child-bearing potential) will be conducted at Screening, Baseline, and all subsequent study visits. A positive pregnancy test will exclude the subject from further participation in the study. Pregnant subjects who are discontinued from the study will be transitioned to an alternate therapy at the discretion of the Investigator.

3.3.2.5 Adverse Events

Adverse Events will be recorded throughout the course of the study from the time that each subject and/or caregiver signs the informed consent/assent form until the time screen failure is documented, or until the subject is either discontinued from the study or all Week 24 study assessments have been completed. Each subject/caregiver will be directly questioned for AEs at each scheduled study visit and during required telephone contacts. Subjects/caregivers will also be instructed to spontaneously report all AEs throughout the study. Additionally, a detailed collection of prostacyclin-related AEs will be captured via a standardized diary completed by the subject and/or caregiver each day of the five day inpatient hospital stay during the transition from IV/SC Remodulin to oral treprostinil or all subjects in Cohort 1.

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 30 days if the AE extends beyond the final study visit. All AEs meeting the criteria for serious (i.e., serious adverse events [SAEs]) should 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.

All AEs/SAEs that occur while the subject is on oral treprostinil will be recorded as instructed in this protocol (Section 9.3).

If, at any time, the subject withdraws from the study and/or changes from study drug to commercially available Orenitram, any AEs/SAEs that occur on Orenitram (including product use errors, product quality problems, and therapeutic failures) will be reported following local post-marketing reporting requirements. These events will not be included in the eCRF.

Pulmonary arterial hypertension symptoms (Section 3.3.1.4) and PAH disease related events (Section 9.1.4) should only be recorded as an AE if the event is serious, new, or unusual with respect to intensity, frequency, or duration as compared to symptoms in the subject's medical history; or there is a reasonable possibility that the event was caused by the study drug.

3.3.2.6 Telephone Contact (All Cohorts)

Daily telephone contact (excluding weekends for all subjects and inpatient hospital stay for Cohort 1 subjects) is required for the first two weeks of the study. Weekly telephone contact is required from the Week 3 visit until the Week 12 visit and then at least every other week until the Week 24 visit.

The purpose of the telephone contact is to instruct the subject/caregiver to titrate their dose of oral treprostinil and assess for AEs and concomitant medications. Subject/caregiver may be contacted via email in lieu of a telephone call; however, email should not replace direct follow-up by telephone or in clinic for clinical significant AEs or other emergent issues. All telephone or email contacts (i.e. any dosing instructions, AEs reported and/or medication changes) with the subject must be noted in the source documentation.

3.3.2.7 Continued Access Plan

Subjects who have completed the Week 24 Visit will be given the option for continued access to oral treprostinil. During the Week 24 Visit, the Investigator should assess each subject's eligibility for the Continued Access Plan.

3.3.3 Pharmacokinetics or Other Special Study

3.3.3.1 Pharmacokinetic Sampling

Pharmacokinetic blood sampling will occur twice for each subject in Cohort 1; once during Baseline while the subject is still receiving IV/SC Remodulin prior to starting oral treprostinil, and again at Week 24 when the subject has reached a stable dose of oral treprostinil. Subjects in Cohort 2 and 3 will undergo PK blood sampling at Week 24 only.

All blood samples should be drawn within a ±10 minute window from their scheduled time point. Record the time and reason for late blood draws and document hemolyzed samples in the eCRF. Hemolyzed blood samples may be redrawn as able. Pharmacokinetic parameters derived from treprostinil plasma concentration-time data will be determined for each subject.

Appendix 15.5 contains a detailed description for the PK blood collection, processing, storage, and shipment of all samples.

Baseline PK Assessment (Cohort 1 Only):

At Baseline subjects in Cohort 1 will undergo an 8-hour PK assessment while receiving IV/SC Remodulin within seven days prior to the first dose of oral treprostinil. Blood samples will be obtained from each subject at time 0 and the following subsequent time points: 4 and 8 hours after time 0 for a total of three blood samples. During the Baseline phase, time 0 should be at the same time of day that it is estimated the Week 24 morning oral treprostinil dose will occur (i.e., if the subject/caregiver anticipates the first daily dose of oral treprostinil at Week 24 will be administered at 8 AM, time 0 should be 8 AM).

Baseline PK Assessment Sample Timelines:

Baseline Time Points	Sample Time of Day	Comment (Cohort 1 subjects only while on IV/SC Remodulin)
Time 0	8:00	Estimated time that the morning dose of oral treprostinil will occur at the Week 24 PK assessment.
4 hours	12:00	All subsequent blood draws should occur within a ±10 minute window from their scheduled time point. At Baseline all blood draws should be based off of time 0.
8 hours	16:00	

Week 24 PK Assessment (All Cohorts):

At Week 24 all subjects (all cohorts) will undergo an 8-hour PK assessment while receiving oral treprostinil. No oral treprostinil dose changes are allowed within five days of the Week 24 PK sampling, unless required to protect subject safety. All subjects on a TID dosing regimen will undergo the Week 24 PK assessment based on the first daily dose (morning dose) of oral treprostinil. If a subject is on a QID dosing regimen, the Investigator may conduct the PK assessment based on the first daily dose (morning dose) or the second daily dose (midday dose) at their discretion. The PK assessment dose of oral treprostinil will be taken in the clinic and should occur approximately 8 hours after the prior evening's last oral treprostinil dose for subjects using the morning dose for the PK assessment. When using the midday dose for the PK assessment, the midday dose of oral treprostinil should occur approximately 4 to 6 hours after that day's morning dose.

Blood samples will be obtained from each subject at pre-dose (immediately prior [i.e., 10 minutes ±5 minutes] to administration of the PK assessment dose of oral treprostinil) and the following time points: 2, 4, 6, and 8 hours after the PK assessment dose of oral treprostinil (all time points will be based off of the time the PK assessment dose is administered). No other doses of oral treprostinil should be taken during the PK sampling period if the subject is on a TID regimen. The second daily dose of oral treprostinil (midday dose) on a TID regimen will be taken in the clinic and after the final 8-hour PK sample is collected. Subjects on a QID oral treprostinil regimen will take their next daily dose (midday dose or early evening dose [PM #1 dose] based on timing of PK assessment dose) between the 4 and 6 hour time points of the PK sampling (±10 minutes). The PK assessment dose of oral treprostinil must be observed in the clinic by study personnel and taken with food. A

brief description of the food ingested prior to the PK dose of oral treprostinil administration should be recorded in the source and eCRF. Tablets must not be chewed or broken.

Week 24 TID PK Assessment Sample Timelines:

Week 24 Time Points	Sample Time of Day	Comment (all cohorts while on oral treprostinil)
Previous evening dose	24:00	The previous evening last dose at the Week 24 PK assessment should be taken approximately 8 hours prior to the next morning oral treprostinil dose.
Pre-dose	7:50	Blood draw should occur 10 minutes ±5 minutes prior to the morning dose of oral treprostinil.
Morning dose	8:00	The morning dose at the Week 24 PK assessment will be taken in the clinic and should occur approximately 8 hours after the prior evening's last oral treprostinil dose.
2 hours	10:00	At Week 24 all blood draws should be based off of the morning dose of oral treprostinil. All subsequent blood draws should occur within a ±10 minute window from their scheduled time point.
4 hours	12:00	
6 hours	14:00	
8 hours	16:00	
Midday dose	16:15	The midday dose should be taken in the clinic with food and after the last PK assessment has been completed.

Week 24 QID PK Assessment Based on Morning Dose Sample Timeline:

Week 24 Time Points	Sample Time of Day	Comment (All cohorts while on oral treprostinil)
Previous evening dose	24:00	The previous evening dose at the Week 24 PK assessment should be taken approximately 8 hours prior to the next morning oral treprostinil dose.
Pre-dose	7:50	Blood draw should occur 10 minutes ±5 minutes prior to the morning dose of oral treprostinil.
Morning dose	8:00	The morning dose at the Week 24 PK assessment will be taken in the clinic and should occur approximately 8 hours after the prior evening's last oral treprostinil dose.
2 hours	10:00	All blood draws should be based off of the morning dose of oral treprostinil. All subsequent blood draws should occur within a ±10 minute window from their scheduled time point. Subjects on QID dosing should take their second daily dose of oral treprostinil (midday dose) between the 4 and 6 hour time points of the PK sampling (±10 minutes)
4 hours	12:00	
6 hours	14:00	
8 hours	16:00	

Week 24 QID PK Assessment Based on Midday Dose Sample Timeline:

Week 24 Time Points	Sample Time of Day	Comment (all cohorts while on oral treprostinil)
Morning dose	6:00	The morning dose on the day of the Week 24 PK assessment should be taken approximately 4 to 6 hours prior to the midday dose of oral treprostinil.
Pre-dose	9:50	Blood draw should occur 10 minutes ±5 minutes prior to the midday dose of oral treprostinil.
Midday dose	10:00	The midday dose at the Week 24 PK assessment will be taken in the clinic and should occur approximately 4 to 6 hours after that day's morning dose of oral treprostinil.
2 hours	12:00	All blood draws should be based off of the midday dose of oral treprostinil. All subsequent blood draws should occur within a ±10 minute window from their scheduled time point. Subjects on QID dosing should take their third daily dose of oral treprostinil (early evening dose [PM #1]) between the 4 and 6 hour time points of the PK sampling (±10 minutes)
4 hours	14:00	
6 hours	16:00	
8 hours	18:00	

3.3.3.2 Cardiac Magnetic Resonance Imaging (cMRI)

Cardiac MRI imaging will be performed in all subjects aged 10 years and older at Baseline and Week 24/Premature Termination; imaging may be optionally performed in subjects under the age of 10 years. Cardiac MRI should be performed prior to the 6MWT and CPET, if done on the same day. If subject requires anti-anxiety medication in order to undergo and still follow directions (no general anesthesia) during the cMRI (without contrast), then the cMRI should be performed on a separate day from the CPET and 6MWT.

The subject's BP will be taken immediately prior to the cMRI assessment in the supine position to measure vascular parameters.

The following parameters will be evaluated:

- Right ventricular (RV) mass index
- RV ejection fraction (RVEF)
- Left ventricular (LV) ejection fraction (LVEF)
- RV end-diastolic volume (RVEDV) index
- RV end-systolic volume (RVESV) index

- RV stroke volume index
- LV stroke volume index
- RV cardiac output index

The following additional parameters may be collected:

- Flow pattern through the MPA by phase-sensitive gradient echo imaging
- Flow pattern through the RPA by phase-sensitive gradient echo imaging
- Flow pattern through the Ascending aorta by phase-sensitive gradient echo imaging
- RV:LV end-systolic diameter ratio
- Systolic septal flattening
- Right atrial size
- Presence of congenital heart disease
- Atrial or ventricular shunt

Cardiac MRI measurements from images will be analyzed by a centralized specialist reader to control for bias and to reduce inter-reader variability. The centralized specialist reader may communicate with the site and establish study specific analysis settings for assessments performed for purposes of this protocol.

3.4 NUMBER OF CENTERS

The study is a US-based multi-center study with approximately 10 centers participating.

3.5 NUMBER OF SUBJECTS

A total of 40 subjects will be enrolled in this study. Approximately 25 subjects will be enrolled between Cohort 1 and Cohort 2 of this study, and 15 subjects will be enrolled into Cohort 3.

3.6 ESTIMATED STUDY DURATION

From Screening until study completion, expected duration of subject participation is approximately 28 weeks (four week screening period and 24 week treatment period).

4 SUBJECT ELIGIBILITY

Inclusion and exclusion criteria are to be assessed during the Screening period and reconfirmed at the Baseline visit prior to the first dose of oral treprostinil. Study related procedures must be conducted during the Screening period after obtaining informed consent and assent (if applicable) to determine subject eligibility for the study.

4.1 INCLUSION CRITERIA

A subject is eligible for inclusion in this study if all of the following criteria apply:

1. Legal guardian informed consent and subject assent, if appropriate, to participate in the study is voluntarily given.
2. The subject is between 7 and 17 years of age, inclusive, on the date informed consent is signed.
3. ***Cohort 3:*** The subject must weigh a minimum of 22 kg at Screening.
4. The subject has a current diagnosis of PAH (WHO Group I) associated with:
    a. Idiopathic or heritable PAH
    b. Persistent PAH for at least one year following surgical repair of a congenital systemic-to-pulmonary cardiac shunt, congenital heart disease, or other congenital heart lesions with no clinically significant residual defects and condition is stabilized hemodynamically
    c. PAH in subjects with unrepaired restricted atrial septal defect, ventricular septal defect, or patent ductus arteriosus; subject must have a resting post-ductal oxygen saturation (off oxygen) of greater than 88%
5. The subject has a current diagnosis of PAH confirmed by right heart catheterization (RHC) prior to the Screening visit with the following parameters:
    a. Mean pulmonary arterial pressure (mPAP) of ≥25 mmHg
    b. Pulmonary vascular resistance index (PVRi) of >3 Wood Units * m^2
    c. Left ventricular end diastolic pressure (LVEDP) or pulmonary capillary wedge pressure (PCWP) of ≤15 mmHg

6. ***Cohort 1:*** The subject must have been receiving IV/SC Remodulin for at least 90 days without dose change for at least 30 days prior to Baseline. The IV/SC Remodulin dose will be between 25-75 ng/kg/min, inclusive, for the first five subjects in the cohort. Following a safety review, the dose range may be expanded to 25-125 ng/kg/min, inclusive, for the remaining subjects. Subjects must be receiving stable doses of all other PAH medications for at least 14 days prior to the Baseline assessments; exception for diuretics and anticoagulants as outlined in Section 4.3.1.

7. ***Cohort 2:*** The subject must have been receiving inhaled prostacyclin for at least 90 days and has been at the current stable dose without changes for at least 30 days prior to Baseline. Subjects must be receiving stable doses of all other PAH medications for at least 14 days prior to the Baseline assessments; exception for diuretics and anticoagulants as outlined in Section 4.3.1.

8. ***All Cohorts:*** All subjects must be optimally treated (as determined by the Investigator) with background PAH therapies (e.g., PDE-5i, ERA, soluble guanylate cyclase [sGC]) for at least 90 days and have been on a stable dose without changes (except documented weight based adjustments) for at least 30 days prior to the first dose of oral treprostinil. Subjects must be receiving stable doses of all other PAH medications for at least 14 days prior to the first dose of oral treprostinil; exception for diuretics and anticoagulants as outlined in Section 4.3.1.

9. The subject is willing and able to swallow intact tablets whole without chewing, breaking, or splitting.

10. The subject is willing and able to comply with the dietary requirements associated with the oral treprostinil dosing regimen.

11. The subject must be on stable doses of other medical therapy for 14 days prior to Baseline visit with no dose adjustments, additions, or discontinuations. Dose changes of diuretics are allowed if within the usual dose adjustments prescribed for the subject. Anticoagulants may be adjusted, but not discontinued or added, within 14 days of

Baseline. Temporary discontinuation of anticoagulants when related to study related procedures is allowed.

12. Females of childbearing potential include any female who has experienced menarche. Females of childbearing potential must practice true abstinence from intercourse, have an IUD, or must use two different forms of highly effective contraception for the duration of the study, and for at least 30 days after discontinuing oral treprostinil. Medically acceptable forms of effective contraception include approved hormonal contraceptives (such as birth control pills) or barrier methods (such as a condom or diaphragm) used with a spermicide. For females of childbearing potential, a negative urine pregnancy test is required at Baseline prior to oral treprostinil administration. Males participating in the study must use a condom during intercourse for the duration of the study, and for at least 48 hours after discontinuing oral treprostinil.

13. Subjects with a history of metallic implants, prior neurosurgical clip placement, or other potential contraindications to cMRI may be individually evaluated per site standard operating procedures for MRI performance.

14. In the opinion of the Principal Investigator, the subject and/or legal guardian is able to communicate effectively with study personnel, and is considered reliable, willing and likely to be cooperative with protocol requirements, including attending all study visits.

4.2 EXCLUSION CRITERIA

A subject is not eligible for inclusion in this study if any of the following criteria apply:

1. The subject has a diagnosis of large unrestrictive ventricular septal defect or patent ductus arteriosus, Eisenmenger syndrome, congenital diaphragmatic hernia, or a chronic lung disease, such as bronchopulmonary dysplasia, or interstitial lung disease.

2. The subject has a current disease severity of Panama functional class IIIb or IV.

3. The subject has previously been exposed to oral treprostinil.

4. ***Cohort 1:*** the subject has had previous intolerance to treprostinil or epoprostenol due to systemic adverse effects that resulted in discontinuation of therapy. This does not include site pain reactions or central venous catheter-related blood stream infections.

5. ***Cohort 1 and 2:*** the subject is receiving IV/SC Remodulin or Tyvaso (as the inhaled prostacyclin) for any other disease or condition other than the treatment of PAH in accordance with the IV/SC Remodulin or Tyvaso package inserts (i.e., eligible subjects must have a WHO Group I PAH classification as defined in inclusion criteria #4).

6. ***Cohort 3:*** the subject has been previously exposed to a prostacyclin within 30 days of Screening, with the exception of vasoreactivity testing.

7. The subject is pregnant or lactating.

8. The subject has a current diagnosis of uncontrolled sleep apnea as defined by their physician.

9. The subject has severe renal insufficiency as defined by an estimated creatinine clearance (CrCl) <30 mL/min (Schwartz Formula) or the requirement for dialysis at Screening.

10. The subject has moderate to severe hepatic dysfunction; defined as elevated liver function tests (AST or ALT) greater than or equal to three times the upper limit of normal at Screening, or Child Pugh class B or C hepatic disease.

11. The subject has clinically significant anemia as defined by a hemoglobin and/or hematocrit level <75% of the lower limit of normal ranges according to age and gender.

12. The subject has Down Syndrome.

13. The subject has uncontrolled systemic hypertension as evidenced by a systolic or diastolic blood pressure greater than the 95th percentile for age, height, and gender at Screening or Baseline.

14. The subject and/or legal guardian has/have an unstable psychiatric condition or is/are mentally incapable of understanding the objectives, nature, or consequences of the trial, or has any condition in which the Investigator's opinion would constitute an unacceptable risk to the subject's safety.

15. The subject has an active infection, or has any other cardiovascular, liver, renal, hematologic, gastrointestinal, immunologic, endocrine, metabolic, or central nervous system disease or condition that, in the opinion of the Investigator, may adversely affect the safety of the subject or interfere with the interpretation of study assessments.

16. Subject is actively listed for transplantation.

17. The subject is receiving an investigational drug, has an investigational device in place or has participated in an investigational drug or device study within 30 days prior to Baseline. Participation in an observational study does not disqualify a potential subject from study participation.

4.3 PRESCRIBED THERAPY

4.3.1 Concomitant Medications

Cohort 1:

Subjects must have been receiving IV/SC Remodulin for at least 90 days prior to Baseline and have been at the current dose without changes for at least 30 days prior to Baseline.

Cohort 2:

Subjects must have been receiving inhaled prostacyclin for at least 90 days with no dose changes for at least 30 days prior to Baseline.

All Cohorts:

Subjects must be optimally treated (as determined by the Investigator) with background PAH therapies (e.g., PDE-5i, ERA, sGC) for at least 90 days and have been on a stable dose without changes (except documented weight based adjustments) for at least 30 days prior to Baseline. All attempts should be made to avoid dose adjustments of current PAH background therapy(ies) or the addition of another PAH therapy from Baseline to Week 24.

Subjects must be receiving stable doses of all other medications for at least 14 days prior to the Baseline assessments. Dose changes of diuretics are allowed if the dose adjustments are within the usual dose adjustments prescribed for the subject. Dose adjustments of anticoagulants are permitted at any time during the study, as needed. Anticoagulants may be temporarily discontinued during the study if necessary for the safety of study related or medically required procedures (e.g., RHC).

For the purposes of the 6MWT, if the subject was assessed at Baseline using oxygen therapy, then all 6MWTs during the 24-week study should be conducted with the same oxygen flow rate and mode of administration. All concomitant medications taken during the conduct of the study, including those taken for AEs or other medical events, must be recorded in the subject's source documents and transcribed as required to the eCRF. Dose changes of concomitant medications will not be captured in the eCRF.

5 SUBJECT ENROLLMENT

5.1 TREATMENT ASSIGNMENT

All subjects will receive treatment with oral treprostinil. Subjects will be enrolled into a cohort based on their current PAH treatment regimen.

5.2 RANDOMIZATION

No randomization will occur.

5.3 BLINDING

This an open-label study; all subjects will receive oral treprostinil extended release tablets.

5.4 STOPPING CRITERIA

If any of the following events occur within the four weeks following the first dose of drug oral treprostinil given for all cohorts, the subject should be transitioned back to IV/SC Remodulin (Cohort 1 subjects only) or tapered off oral treprostinil, as appropriate, and discontinued from the study:

- Unplanned hospitalization as a result of worsening PAH
- Clinically significant worsening in PAH symptoms or signs, which the Investigator feels requires a change of current therapy.

If two or more of the first five subjects in any cohort meet the stopping criteria, the data will be reviewed by a Data Safety Monitoring Board (DSMB) prior to enrolling additional subjects into that cohort.

If any of these events happen after the first four weeks of the study, it is not required that a subject be removed from the study. The Investigator will determine whether it is safe for a subject to remain in the study.

6 DRUGS AND DOSING (OR TREATMENT PROCEDURES)

6.1 DRUG DOSAGE, ADMINISTRATION AND SCHEDULE

Oral treprostinil will be provided as 0.125 mg (blue), 0.25 mg (green), 1 mg (yellow) or 2.5 mg (pink) extended release tablets. Subjects/caregivers must be instructed to take the appropriate amount of 0.125 mg, 0.25 mg, 1 mg and/or 2.5 mg tablets based upon their prescribed dose.

Oral treprostinil will be dosed TID or QID at the discretion of the Investigator, with food. Dosing will take place approximately every 6 to 8 hours for TID dosing or approximately every 4 to 6 hours for QID dosing, with adjustments permitted based on the subject's lifestyle and schedule. Study subjects should take their study drug at approximately the same time 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 in order to be monitored for the onset of symptoms due to possible inappropriate drug release.

For subjects receiving oral treprostinil TID, dosing frequency may be adjusted from TID to QID if clinically indicated, at the discretion of the Investigator. For applicable subjects, it is recommended, but not required, to take the total daily dose during TID dosing, and divide the total daily dose into a QID regimen using the closest, or lower, tablet strength as seen in the example table below. Dose modifications should always occur in accordance with Investigator judgment.

Example Transition from TID to QID Dosing of Oral Treprostinil

TID Dosing Regimen	Total Daily Dose with TID Dosing	QID Dosing Regimen	Total Daily Dose with QID Dosing
1.75 mg TID	5.25 mg	1.25 mg QID	5 mg
2.5 mg TID	7.5 mg	1.875 mg QID	7.5 mg
3.75 mg TID	11.25 mg	2.75 mg QID	11 mg
5.5 mg TID	16.5 mg	4.125 mg QID	16.5 mg
8.25 mg TID	24.75 mg	6.125 mg QID	24.5 mg
10 mg TID	30 mg	7.5 mg QID	30 mg

6.1.1 Cohort 1: IV/SC Remodulin to Oral Treprostinil Transition

Once all entry criteria have been met and Baseline assessments completed, subjects should begin transition in the hospital from IV/SC Remodulin to oral treprostinil with a goal for complete transition off of IV/SC Remodulin within five days of the start of the transition. If possible, Day 5 (or final day of hospital stay if transition occurred in less than 4 days) of hospital stay should be reserved as an observational period for subjects successfully transitioned to oral treprostinil and no longer receiving IV/SC Remodulin. A cross titration will occur so that the dose of IV/SC Remodulin is decreased as the dose of oral treprostinil is increased. Once subjects have been transitioned off IV/SC Remodulin, the dose of oral treprostinil may continue to be titrated to the appropriate optimal dose for that subject throughout the rest of the study.

Dosing guidelines:

- The following equation can be used to estimate a comparable total daily dose of oral treprostinil (in mg) using the subject's dose of IV/SC Remodulin (in ng/kg/min) and weight (in kg):

Oral treprostinil total daily dose (mg) = 0.0072 x Remodulin dose (ng/kg/min) x weight

- IV/SC Remodulin should not be decreased more than 30 ng/kg/min within a 24 hour period
- Oral treprostinil should be increased in proportion to Remodulin decreases and the subject's weight
- IV/SC Remodulin doses should be adjusted (i.e., decreased) at the same time oral treprostinil dose is increased

Example TID Dosing Schedule for a 35 kg Subject:

Hospital Day	IV/SC Remodulin (ng/kg/min)	Oral Treprostinil (mg)
Day 1 (0-24 hours)		
Morning (upon admission)	65	0
Midday	59	0.5
Evening	53	1
Day 2 (24-48 hours)		
Morning	47	1.5
Midday	41	2
Evening	35	2.5
Day 3 (48-72 hours)		
Morning	29	3
Midday	23	3.5
Evening	17	4.
Day 4 (72-96 hours)		
Morning	11	4.5
Midday	5	5
Evening	0	5.5 (target dose)
Day 5 (96-120 hours): Observational period prior to hospital discharge		
Morning	0	continue to titrate if appropriate
Midday	0	continue to titrate if appropriate
Evening	0	continue to titrate if appropriate

Example QID Dosing Schedule for a 35 kg Subject:

Hospital Day	IV/SC Remodulin (ng/kg/min)	Oral Treprostinil (mg)
Day 1 (0-24 hours)		
Morning (upon admission)	65	0
Midday	61	0.25
Early Evening (PM #1)	57	0.5
Late Evening (PM #2)	53	0.75
Day 2 (24-48 hours)		
Morning	48	1.125
Midday	44	1.375
Early Evening (PM#1)	40	1.625
Late Evening (PM #2)	36	1.875
Day 3 (48-72 hours)		
Morning	30	2.25
Midday	26	2.5
Early Evening (PM #1)	22	2.75
Late Evening (PM #2)	18	3
Day 4 (72-96 hours)		
Morning	12	3.375
Midday	8	3.625
Early Evening (PM #1)	4	3.875
Late Evening (PM #2)	0	4.125 (target dose)
Day 5 (96-120 hours): Observational period prior to hospital discharge		
Morning	0	continue to titrate if appropriate
Midday	0	continue to titrate if appropriate
Early Evening (PM #1)	0	continue to titrate if appropriate
Late Evening (PM #2)	0	continue to titrate if appropriate

If necessary for subject safety, the transition from IV/SC Remodulin may extend beyond five days. Extended transitions must occur in hospital or subject must be willing and able to return to clinic as needed until the transition is complete. The transition must be completed by Week 4, or the subject will be withdrawn from the study. Once a subject has completely transitioned off IV/SC Remodulin, dose escalations of oral treprostinil should occur in either 0.125 mg or 0.25 mg increments every 24 hours, as tolerated. Sudden dose escalation or

reductions should be avoided as they may lead to intolerable adverse effects or worsening of PAH. Gradual dose titrations are recommended to reduce the risk to subjects.

Routine contact between site personnel and the subject/caregiver should be conducted to monitor AEs and make decisions about dose titration between scheduled study visits. Dose changes may be made at any time up until five days prior to the Week 24 visit. Week 24 visit assessments can be performed over five days (120 hours) if needed; however, no oral treprostinil dose adjustments are allowed from five days prior to the Week 24 study visit, unless required to protect subject safety. All dose changes will be documented and captured in the eCRF.

6.1.2 Cohort 2: Inhaled Prostacyclin to Oral Treprostinil Transition

Once all entry criteria have been met and Baseline assessments completed, dosing of oral treprostinil will be initiated at 0.125 mg TID or QID at the discretion of the Investigator, with food. Dosing will take place approximately every 6 to 8 hours for TID dosing or approximately every 4 to 6 hours for QID dosing, with adjustments permitted based on the subject's lifestyle and schedule. The first dose of 0.125 mg oral treprostinil should be taken at the study site. A cross titration will occur so that doses of inhaled prostacyclin will be decreased as oral treprostinil is increased. The transition must be completed by Week 4, or the subject will be withdrawn from the study.

Oral treprostinil dose escalations may occur every 24 hours (following three or four consecutive doses depending on TID or QID dosing, respectively) and should occur in increments of 0.125 mg TID or QID, at the discretion of the Investigator, during the first four weeks of the study as clinically indicated. Following four weeks of treatment, dose escalations may occur in either 0.125 mg or 0.25 mg increments every 24 hours, as tolerated. Sudden dose escalations or reductions should be avoided as they may lead to intolerable adverse effects or worsening of PAH. Gradual dose titrations are recommended to reduce the risk to subjects.

Routine contact between site personnel and the subject/caregiver should be conducted to monitor AEs and make decisions about dose titration between scheduled study visits. Dose

changes may be made at any time up until five days prior to the Week 24 visit. Week 24 visit assessments can be performed over five days (120 hours) if needed; however, no oral treprostinil dose adjustments are allowed from five days prior to the Week 24 study visit, unless required to protect subject safety. All dose changes will be documented and captured in the eCRF.

6.1.3 Cohort 3: Addition of Oral Treprostinil to Background PAH Therapy (De Novo Prostacyclin Subjects)

Once all entry criteria have been met and Baseline assessments completed, dosing of oral treprostinil will be initiated at 0.125 mg TID or QID at the discretion of the Investigator, with food. Dosing will take place approximately every 6 to 8 hours for TID dosing or approximately every 4 to 6 hours for QID dosing, with adjustments permitted based on the subject's lifestyle and schedule. The first dose of 0.125 mg oral treprostinil should be taken at the study site.

Dose escalations may occur every 24 hours (following three or four consecutive doses depending on TID or QID dosing, respectively) and should occur in increments of 0.125 mg TID or QID at the discretion of the Investigator during the first four weeks of the study as clinically indicated. Following four weeks of treatment, dose escalations may occur in either 0.125 mg or 0.25 mg increments every 24 hours, as tolerated. Sudden dose escalation or reductions should be avoided as they may lead to intolerable adverse effects or worsening of PAH. Gradual dose titrations are recommended to reduce the risk to subjects.

Routine contact between site personnel and the subject/caregiver will be conducted to monitor AEs and make decisions about dose titration between scheduled study visits. Dose changes may be made at any time up until five days prior to the Week 24 visit. Week 24 visit assessments can be performed over five days (120 hours) if needed; however, no oral treprostinil dose adjustments are allowed from five days prior to the Week 24 study visit, unless required to protect subject safety. All dose changes will be documented and captured in the eCRF.

6.1.4 Dosing Interruptions

Subjects must not "make-up" or double-up on missed doses. If dosing is interrupted for longer than 24 hours, consideration should be given to re-titrating the subject's dose gradually to the last dose that was administered prior to the dose interruption, particularly in cases where the last dose prior to interruption was greater than 3 mg. The upward "re-titration" in such instances may, at the Investigator's discretion, be more rapid than the subject's initial dose titration.

In the event of a planned short-term treatment interruption for subjects unable to take oral medications, consider a temporary infusion of SC or IV treprostinil. To calculate the total daily dose (mg) of treprostinil for the parenteral route use the following equation:

Remodulin (ng/kg/min) = (139 x oral treprostinil total daily dose (mg) / weight (kg)

6.2 ACCESS TO BLINDED TREATMENT ASSIGNMENT

This is an open-label study; all subjects will receive treatment with oral treprostinil extended release tablets.

6.3 COMPLIANCE

Each subject/caregiver will be provided with a dosing diary in order to record dosing information throughout the study. Compliance with oral treprostinil will be assessed at Week 3, 6, 12, and 24/Premature Termination visits, as applicable. At scheduled visits, subjects should be instructed to bring all oral treprostinil to the investigational site.

Upon return of oral treprostinil (study drug) at Weeks 3, 6, 12, 24/Premature Termination, as applicable, the study coordinator or pharmacist must document the number of returned tablets of each strength and determine if the appropriate amount of oral treprostinil remains based upon the dose of oral treprostinil prescribed. Compliance will be determined by comparing the doses that the subject reports taking in their dosing diary to the amount of oral treprostinil returned to the site. Open bottles of oral treprostinil returned at Weeks 3, 6, 12, and 24/Premature Termination will not be re-dispensed to the subject. Any unopened bottles of oral treprostinil may be re-dispensed to the subject and site personnel will dispense additional

new supply of oral treprostinil at Weeks 3, 6, and 12 for the subsequent interval. If necessary, additional oral treprostinil may be dispensed in between protocol-required visits.

Each subject/caregiver will also be asked at each visit whether he or she has been compliant with dosing instructions. Continued non-compliance may lead to withdrawal of the subject from the study, after consultation between the Investigator and the Sponsor.

7 EXPERIMENTAL PROCEDURES

7.1 SCREENING PHASE (ALL COHORTS)

The Screening phase can begin up to 28 days prior to the Baseline visit. Prior to the Baseline visit site personnel should complete a Pre-Baseline Review Form for review by the Medical Monitor prior to moving forward with any Baseline visit assessments.

The recommended sequence of assessments for the Screening visit is as follows (if not combined with the Baseline visit):

- Informed consent/assent
- Inclusion/exclusion criteria review
- Demographics
- PAH history
- Medical history
- Vital signs (following at least five minutes of rest; collected prior to 6MWT or at least 30 minutes following 6MWT); including height
- Urine pregnancy test (females of child bearing potential)
- Physical examination
- Panama and WHO functional classification
- Practice 6MWT/ Borg dyspnea score (only required if subject has not previously performed a 6MWT at the study site; 6MWT to be conducted following at least five minutes of rest and Borg dyspnea score to be conducted immediately following 6MWT)
- Clinical laboratory parameters
- Adverse events
- Concomitant medications

- Complete Pre-Baseline Review Form and submit to Sponsor for permission to move forward with the Baseline visit assessments

7.2 BASELINE VISIT (ALL COHORTS)

The Baseline assessments can be conducted over five days (120 hours) prior to the first dose of oral treprostinil. Pharmacokinetic assessments (Cohort 1 subjects only) may be scheduled up to seven days prior to the first dose of oral treprostinil. Pharmacokinetic assessments at Baseline will not be conducted in Cohort 2 or Cohort 3 subjects. The recommended sequence of assessments for Baseline visit is as follows (if not combined with Screening visit):

- PedsQL questionnaire (must be performed as first assessment prior to seeing their physician or healthcare provider or completing any other forms or assessments)
- Vital signs (following at least five minutes of rest; collected prior to 6MWT or at least 30 minutes following 6MWT)
- Urine pregnancy test (females of child bearing potential)
- Clinical laboratory parameters
- NT-pro-BNP (prior to 6MWT or CPET and first dose of oral treprostinil)
- 12-lead ECG (following at least five minutes of rest in the semi-recumbent position)
- PAH symptoms
- Panama and WHO functional classification
- Inclusion/exclusion criteria review
- Cardiac MRI (must be performed prior to the 6MWT and CPET if done on the same day; if subject requires anti-anxiety medication (no general anesthesia) during the cMRI (without contrast), then the cMRI should be performed on a separate day from the CPET and 6MWT
- 6MWT/Borg dyspnea score (must be conducted prior to the first dose of oral treprostinil), includes oximetry and HR recovery monitoring (to be conducted following at least five minutes of rest); Borg dyspnea score to be conducted immediately following 6MWT)
- CPET (if performed on same day as 6MWT, CPET should be conducted a minimum of two hours after 6MWT)

- Pharmacokinetics ([Cohort 1 subjects only] Section 3.3.3; may be conducted seven days prior to the first dose of oral treprostinil)
- Dispense oral treprostinil, and provide subject diary/dosing instructions
- First administration of oral treprostinil with food (Cohort 1 subjects will be admitted for an inpatient hospital stay for the transition)
- Adverse events
- Concomitant medications

7.3 COMBINED SCREENING AND BASELINE (ALL COHORTS)

Screening and Baseline visits may be combined if all assessments are completed and entry criteria satisfied within five days (120 hours) prior to the first dose of oral treprostinil. Prior to the first Baseline assessment, site personnel should complete a Pre-Baseline Review Form for review by the Medical Monitor prior to moving forward with any Baseline visit assessments. The recommended sequence of assessments for a combined Screening and Baseline visit is as follows:

Assessments to be completed as part of the Screening phase:

- Informed consent/assent
- PedsQL questionnaire (must be performed as first assessment prior to seeing their physician or healthcare provider or completing any other forms or assessments)
- Inclusion/exclusion criteria review
- Clinical laboratory parameters (enough blood should be drawn for local laboratory to confirm entry criteria of CrCl [Schwartz Formula], AST, ALT, and hemoglobin and/or hemocrit has been met, as well as for the complete panel for central laboratory processing)
- NT-pro-BNP (prior to 6MWT or CPET and first dose of oral treprostinil; for central laboratory)
- Urine pregnancy test (females of child bearing potential)
- Physical examination
- Vital signs (following at least five minutes of rest; collected prior to 6MWT or at least 30 minutes following 6MWT); including height

- Demographics
- PAH history
- Medical history

At this time, the Pre-Baseline Review Form and must be submitted to the Sponsor. Do not proceed with any of the following assessments until you receive the form back from the Sponsor with permission to move forward.

Assessments to be completed as part of the Baseline phase:

- PAH symptoms
- Panama and WHO functional classification
- Cardiac MRI (must be performed prior to the 6MWT and CPET if done on the same day; if subject requires anti-anxiety medication (no general anesthesia) during the cMRI (without contrast), then the cMRI should be performed on a separate day from the CPET and 6MWT
- 12-lead ECG (following at least five minutes of rest in the semi-recumbent position)
- 6MWT/Borg dyspnea score (must be conducted prior to the first dose of oral treprostinil), includes oximetry and HR recovery monitoring (to be conducted following at least five minutes of rest); Borg dyspnea score to be conducted immediately following 6MWT); if subject requires a practice 6MWT, the test must be conducted and precede the Baseline 6MWT by at least one day.
- CPET (if performed on same day as 6MWT, CPET should be conducted a minimum of two hours after 6MWT)
- Pharmacokinetics ([Cohort 1 only] Section 3.3.3, may be conducted seven days prior to the first dose of oral treprostinil)
- Dispense oral treprostinil, and provide subject diary/dosing instructions
- First administration of oral treprostinil with food [Cohort 1 subjects will be admitted for an inpatient hospital stay for the transition]
- Adverse events
- Concomitant medications

7.4 TREATMENT PHASE

The following visits will be conducted in subjects during the 24-week study duration. If the subject is in the hospital during one of the scheduled study visits, the assessments for that visit will be conducted as scheduled during the defined visit window.

7.4.1 Week 0/ Study Days 1-5 (Cohort 1 Only: IV/SC Remodulin to Oral Treprostinil Transition)

The subject will be admitted to the hospital prior to initiating the transition from IV/SC Remodulin to oral treprostinil. Day 1 signifies the day of the first dose of oral treprostinil. For each day (Days 2-5) of the hospital stay, the following assessments will take place:

- Vital signs (following at least five minutes of rest; collected prior to 6MWT or at least 30 minutes following 6MWT)
- PAH symptoms
- 6MWT/Borg dyspnea score (should occur within 2-6 hours of the subject's last dose of oral treprostinil),includes oximetry and HR recovery monitoring (to be conducted following at least five minutes of rest); Borg dyspnea score to be conducted immediately following 6MWT)
- Dose adjustments of oral treprostinil and IV/SC Remodulin (TID or QID, as appropriate)
- Adverse events (including daily administration of a detailed prostacyclin-related adverse events questionnaire)
- Concomitant medications

If the subject stays in the hospital longer than five days, these assessments do not need to be collected on the days beyond Day 5; with the exception of dose adjustments, collection of AEs and changes in concomitant medications which must be collected for the duration of the hospital stay. Following discharge from the hospital, subjects/caregivers will be contacted daily (excluding weekends) via telephone or email by a member of the study team for the first two weeks of the study.

7.4.2 Week 3 Visit (All Cohorts)

During this visit, the recommended sequence of assessments is as follows:

- Vital signs (following at least five minutes of rest; collected prior to 6MWT or at least 30 minutes following 6MWT)
- Urine pregnancy test (females of childbearing potential)
- PAH symptoms
- Panama and WHO functional classification
- 6MWT/Borg dyspnea score (should occur within 2-6 hours of the subject's last dose of oral treprostinil),includes oximetry and HR recovery monitoring (to be conducted following at least five minutes of rest); Borg dyspnea score to be conducted immediately following 6MWT)
- Oral treprostinil (study drug) accountability, and provide subject diary/dosing instructions
- Dose adjustments of oral treprostinil and IV/SC Remodulin/inhaled prostacyclin (if appropriate)
- Adverse events
- Concomitant medications

After the visit, weekly contact between the site and subject/caregiver will continue until the Week 6 study visit.

7.4.3 Week 6 Visit (All Cohorts)

During this visit, the recommended sequence of assessments is as follows:

- Vital signs (following at least five minutes of rest; collected prior to 6MWT or at least 30 minutes following 6MWT)
- Urine pregnancy test (females of childbearing potential)
- PAH symptoms
- Panama and WHO functional classification
- 6MWT/Borg dyspnea score (should occur within 2-6 hours of the subject's last dose of oral treprostinil),includes oximetry and HR recovery monitoring (to be conducted

following at least five minutes of rest); Borg dyspnea score to be conducted immediately following 6MWT)
- Oral treprostinil accountability, and provide subject diary/dosing instructions
- Dose adjustments of oral treprostinil
- Adverse events
- Concomitant medications

After the visit, weekly contact between the site and subject/caregiver will continue until the Week 12 visit.

7.4.4 Week 12 Visit (All Cohorts)

During this visit, the recommended sequence of assessments is as follows:

- PedsQL questionnaire (must be performed as first assessment and as best as possible prior to seeing their physician or healthcare provider or completing any other forms or assessments)
- Vital signs (following at least five minutes of rest; collected prior to 6MWT or at least 30 minutes following 6MWT)
- Urine pregnancy test (females of childbearing potential)
- Clinical laboratory parameters
- NT-pro-BNP (collected prior to 6MWT)
- PAH symptoms
- Panama and WHO functional class
- 6MWT/Borg dyspnea score (should occur within 2-6 hours of the subject's last dose of oral treprostinil),includes oximetry and HR recovery monitoring (to be conducted following at least five minutes of rest); Borg dyspnea score to be conducted immediately following 6MWT)
- Oral treprostinil accountability, and provide subject diary/dosing instructions
- Dose adjustments of oral treprostinil, as needed
- Adverse events
- Concomitant medications

After the visit, contact between the site and subject/caregiver will occur at least every other week until the Week 24 visit.

7.4.5 Week 24 Visit (All Cohorts)

The following assessments will occur during the Week 24 visit. If needed, the visit assessments can be performed over five days (120 hours); however, no oral treprostinil dose adjustments are allowed from five days prior to the Week 24 study visit, unless required to protect subject safety, until all Week 24 visit assessments have been completed.

- PedsQL questionnaire (must be performed as first assessment prior to seeing their physician or healthcare provider or completing any other forms or assessments)
- Pharmacokinetics (Section 3.3.3; may be performed on separate day). No oral treprostinil dose changes are allowed within five days of the Week 24 PK sampling, unless required to protect subject safety.
- Vital signs (following at least five minutes of rest; collected prior to 6MWT or at least 30 minutes following 6MWT)
- Physical examination
- Urine pregnancy test (females of childbearing potential)
- Clinical laboratory parameters
- NT-pro-BNP (prior to 6MWT or CPET)
- 12-lead ECG (following at least five minutes of rest in the semi-recumbent position)
- PAH symptoms
- Panama and WHO functional classification
- Cardiac MRI (must be performed prior to the 6MWT and CPET if done on the same day; if subject requires anti-anxiety medication (no general anesthesia) during the cMRI (without contrast), then the cMRI should be performed on a separate day from the CPET and 6MWT
- 6MWT/Borg dyspnea score (should occur within 2-6 hours of the subject's last dose of oral treprostinil),includes oximetry and HR recovery monitoring (to be conducted following at least five minutes of rest); Borg dyspnea score to be conducted immediately following 6MWT)

- CPET (should be performed 2-6 hours after the morning dose of oral treprostinil [study drug] and prior to the next scheduled dose; if performed on same day as 6MWT, CPET should conducted a minimum of two hours after 6MWT)
- Oral treprostinil accountability
- Adverse events
- Concomitant medications
- Investigator to assess subject's eligibility for the Continued Access Plan

7.4.6 Premature Termination (All Cohorts)

If a subject discontinues from the study prior to Week 24, the following assessments should occur prior to oral treprostinil discontinuation or as soon as possible after. The recommended sequence of assessments is as follows:

- PedsQL questionnaire (must be performed as first assessment and as best as possible prior to seeing their physician or healthcare provider or completing any other forms or assessments)
- Pharmacokinetics (Section 3.3.3, if the subject is still receiving oral treprostinil at the time of discontinuation)
- Vital signs (following at least five minutes of rest; collected prior to 6MWT or at least 30 minutes following 6MWT)
- Urine pregnancy test (females of childbearing potential)
- Clinical laboratory parameters
- NT-pro-BNP (prior to 6MWT or CPET)
- Physical examination
- 12-lead ECG (following at least five minutes of rest in the semi-recumbent position)
- PAH symptoms
- Panama and WHO functional classification
- Cardiac MRI (must be performed prior to the 6MWT and CPET if done on the same day; if subject requires anti-anxiety medication (no general anesthesia) during the cMRI (without contrast), then the cMRI should be performed on a separate day from the CPET and 6MWT

- 6MWT/Borg dyspnea score (should occur within 2-6 hours of the subject's last dose of oral treprostinil),includes oximetry and HR recovery monitoring (to be conducted following at least five minutes of rest); Borg dyspnea score to be conducted immediately following 6MWT)
- CPET (should be performed 2-6 hours after the morning dose of oral treprostinil and prior to the next scheduled dose; if performed on same day as 6MWT, CPET should conducted a minimum of two hours after 6MWT)
- Oral treprostinil accountability
- Adverse events
- Concomitant medications

7.4.7 Continued Access Plan

Subjects who have completed the Week 24 Visit will be given the option for continued access to oral treprostinil (Section 3.3.2.7). During the Week 24 Visit, the Investigator should assess each subject's eligibility for the Continued Access Plan.

8 STUDY TERMINATION

8.1 CRITERIA FOR SUBJECT WITHDRAWAL

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

- Stopping criteria is met
- 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 oral treprostinil (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
- Subject is female and became pregnant during the course of the study

If a subject is discontinued from the study prematurely, the Investigator must provide an explanation in the eCRF and complete the End of Study Record for that subject. If oral treprostinil (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 oral treprostinil 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 30 days if the adverse event extends beyond the final visit.

8.1.1 Lost to Follow-up

If a subject fails to return to clinic or respond after at least three documented attempts by the site to contact the subject by telephone or email, the Investigator should issue a written letter by certified mail requesting the legal guardian and/or caregiver contact the clinic. If no response is received, the subject will be considered lost to follow-up. The site will record the last date of contact in the eCRF as the termination date.

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 Principal Investigator elects to discontinue the study
- The Sponsor elects to discontinue the study at the site
- U.S. FDA regulations are not observed
- The protocol is repeatedly violated
- 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 experience occurring to a subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not it is related to the use of the oral treprostinil (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.
- A worsening of an existing symptom or condition or post-treatment events that occur as a result of protocol-mandated procedures (e.g., exacerbation of a pre-existing illness following the start of the study or an increase in frequency or intensity of a pre-existing episodic event or condition).

Thus, no causal relationship with the study drug is implied by the use of the term "adverse event".

An AE does not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion); however, the condition for which the surgery is required may be an adverse event. Planned surgical measures permitted by the study protocol and the condition(s) leading to these measures are not adverse events.
- Day to day fluctuations of pre-existing disease or conditions present or detected at the start of the study that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic elective surgery, social and/or convenience admissions).
- The disease or disorder being studied or a sign or symptom associated with the disease or disorder unless more severe than expected for the subject's condition.

9.1.2 Suspected Adverse Reaction

Suspected adverse reaction means any AE for which there is a reasonable possibility that the oral treprostinil (study drug) caused the AE. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the oral treprostinil and the AE, as described in Section 15.4.

9.1.3 Serious Adverse Event

A serious adverse event (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 of reaction

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization, but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

9.1.4 Adverse Events Anticipated for PAH

Events associated with disease under study:

Expected events that are related to the disease under study are defined in Table 9-1. These events are anticipated to occur in the study population at some frequency independent of drug exposure.

All events that occur during the course of the study that are included on this list and/or felt to be related to the underlying disease under study by the Investigator should NOT be recorded as an AE unless the event is serious or unusual with respect to intensity, frequency, or duration, or there is a reasonable possibility that it may have been caused by oral treprostinil (study drug). These events should be clearly documented in the subject medical record and identified as signs/symptoms of underlying disease under study. All deaths and unplanned hospitalizations, regardless of underlying cause, will be reported as a SAE.

Table 9-1 Expected Events Attributable to PAH (System Organ Class and PREFERRED Term, Ver. 17.1)

Abdominal pain (Gastrointestinal disorders; ABDOMINAL PAIN)	Hemoptysis (Respiratory, thoracic & mediastinal disorders; HAEMOPTYSIS)
Anorexia (Metabolism and nutrition disorders; DECREASED APPETITE)	Hypoxia (Respiratory, thoracic & mediastinal disorders; HYPOXIA)
Ascites (Gastrointestinal disorders; ASCITES)	Loss of consciousness (Nervous system disorders; LOSS OF CONSCIOUSNESS)
Cardiac arrhythmia (Cardiac disorders; ARRHYTHMIA)	Nausea (Gastrointestinal disorders; NAUSEA)
Cardiac arrest (Cardiac disorders; CARDIAC ARREST)	Edema (General disorders and administration site conditions; OEDEMA)
Heart failure (including exacerbation of) (Cardiac disorders; CARDIAC FAILURE)	Orthopnea (Cardiac disorders; ORTHOPNOEA)
Chest pain (General disorders and administration site conditions; CHEST PAIN)	Pallor (Vascular disorders; PALLOR)
Cardiovascular collapse (Vascular disorders; CIRCULATORY COLLAPSE)	Palpitations (Cardiac disorders; PALPITATIONS)
Cor pulmonale (Cardiac disorders; COR PULMONALE)	Cool extremities (General disorders and administration site conditions; PERIPHERAL COLDNESS)
Cough (Respiratory, thoracic & mediastinal disorders; COUGH)	Pulmonary arterial hypertension, exacerbation of (Vascular disorders; PULMONARY ARTERIAL HYPERTENSION)
Cyanosis (Cardiac disorders; CYANOSIS)	Sudden death (Cardiac disorders; SUDDEN DEATH)
Dizziness (Cardiac disorders; DIZZINESS)	Syncope (Nervous system disorders; SYNCOPE)
Dyspnea at rest (Respiratory, thoracic & mediastinal disorders; DYSPNOEA)	Vasovagal reaction (Nervous system disorders; PRESYNCOPE)
Dyspnea on exertion (Respiratory, thoracic & mediastinal disorders; DYSPNOEA EXERTIONAL)	Tachycardia (Cardiac disorders; TACHYCARDIA)
Paroxysmal nocturnal dyspnea (Cardiac disorders; DYSPNOEA PAROXYSMAL NOCTURNAL)	Vomiting (Gastrointestinal disorders; VOMITING)
Exercise intolerance (General disorders and administration site conditions; EXERCISE TOLERANCE DECREASED)	Weight loss (Investigations; WEIGHT DECREASED)
Fatigue (General disorders and administration site conditions; FATIGUE)	Weight gain (Investigations; WEIGHT INCREASED)

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 related to the AE such as onset and cessation date and times, intensity, seriousness, relationship to oral treprostinil (study drug), and outcome is also to be documented in the eCRF (see Appendix 15.4 for definitions). Where possible, AEs should be recorded using standard medical terminology. The Investigator should attempt, if possible, to establish a diagnosis based on the presenting signs and symptoms. 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.

9.3 FOLLOW UP OF ADVERSE EVENTS

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 30 days 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 lost to follow-up even if they are ongoing more than 30 days 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 any new or additional information as appropriate.

If, at any time, the subject withdraws from the study and/or changes from study drug to commercially available Orenitram, any AEs/SAEs that occur on Orenitram (including product use errors, product quality problems, and therapeutic failures) will be reported following local post-marketing reporting requirements or Continued Access Plan local reporting requirements (Section 3.3.2.7). These events will not be included in the protocol analysis.

Pulmonary arterial hypertension symptoms (Section 3.3.1.4) and PAH disease related events (Section 9.1.4) should only be recorded as an AE if the event is serious, new, or unusual with

respect to intensity, frequency, or duration as compared to symptoms in the subject's medical history; or there is a reasonable possibility that the event was caused by the study drug.

9.4 REPORTING RESPONSIBILITIES OF THE INVESTIGATOR

All SAEs, regardless of expectedness or causality, must be reported to the sponsor within 24 hours of awareness by fax or email [redacted]). A completed SAE Notification Report form along with any relevant hospital records and autopsy reports should be provided to Global Drug Safety at United Therapeutics Corporation. A follow-up SAE Notification Report form must be forwarded to the Global Drug Safety Department at United Therapeutics Corporation within 48 hours of the receipt of any new or updated information. The Investigator must also promptly notify their IRB of the SAE, including any follow-up information, in accordance with applicable national regulations and guidelines set forth by the IRB.

9.5 PREGNANCY

If a study subject becomes pregnant during participation in this clinical study, site staff must notify the sponsor within 24 hours of learning of the pregnancy by completing the Pregnancy Notification Form and submitting via fax or e-mail to Global Drug Safety at United Therapeutics Corporation ([redacted]). The United Therapeutics Global Drug Safety Department will follow-up with the Investigator to ensure appropriate data are provided regarding the outcome of the pregnancy, and to ask the Investigator to update the Pregnancy Notification Form. Pregnancy only becomes an AE/SAE if there is an abnormal outcome, a spontaneous abortion, an elective termination for medical reasons, or a congenital anomaly in the offspring.

9.6 SAFETY REPORTS

In accordance with national regulations, the Sponsor will notify the appropriate regulatory authority(ies), and all participating Investigators of any AE that is considered to be possibly attributable to oral treprostinil (study drug) and is both serious and unexpected. The Investigator must report these AEs to IRBs in accordance with applicable national regulations and guidelines set forth by the IRB.

10 STATISTICAL CONSIDERATIONS

10.1 DATA PROCESSING

The results of all assessments will be transcribed into an eCRF for each subject who signs an ICF until study completion, or study discontinuation for any reason. A representative from the Sponsor will verify eCRF data fields against source documentation. All data transmitted from the site will be reviewed and entered into a quality assured computerized database. Data clarifications will be generated and the database will be edited as appropriate. The eCRF screens are to be reviewed by the Principal Investigator for completeness and accuracy. The Principal Investigator must electronically sign each subject's eCRF to signify their approval of the data. The Principal Investigator will be required to re-sign an eCRF, if changes are made to a subject's eCRF by the site after the Investigator has applied his/her signature. The database will be final when all outstanding queries have been resolved and all data management quality assurance procedures are complete.

10.2 SAMPLE SIZE

This study is intended to provide descriptive data only. A sample size of 40 subjects (25 transition [IV/SC Remodulin and inhaled] subjects and 15 de novo subjects) was selected for feasibility and to provide a reasonably large experience base with which to draw conclusions about the safety of the proposed protocol for (1) transition from moderate to high doses of IV/SC Remodulin to oral treprostinil, (2) transition from inhaled prostacyclin to oral treprostinil, and (3) initiation of oral treprostinil as add-on therapy in de novo prostacyclin subjects. No formal sample size computation was performed with respect to the primary objective of evaluating safety and tolerability as only descriptive reporting of safety data is planned. The planned sample size of 10-15 subjects within a cohort is appropriate for further characterization of the safety, PK and clinical benefit of oral treprostinil in this symptomatic pediatric subject population with PAH.

10.3 ANALYSIS PLAN

No formal hypotheses will be tested. Descriptive statistics will be used to summarize the endpoints and baseline characteristics. For all summaries, all available data will be presented

with no imputation for any missing data. Subjects will contribute the data available up to the point of study completion, or study discontinuation for any reason. Subjects who receive at least one dose of oral treprostinil will be included in the safety analysis population.

10.3.1 Primary Endpoint(s)

The safety and tolerability of transitioning subjects from IV/SC Remodulin to oral treprostinil (Cohort 1) or from inhaled prostacyclin (Cohort 2) will be based on the percentage of subjects successfully transitioning to oral treprostinil. A successful transition is defined as a subject from Cohort 1 or 2 who is receiving oral treprostinil and no longer receiving IV/SC Remodulin or inhaled prostacyclin, respectively at Week 4 and clinically maintained on oral treprostinil treatment through Week 24. A successful initiation of oral treprostinil (Cohort 3) will be defined as a subject who has been clinically maintained on oral treprostinil through Week 24.

10.3.2 Secondary Endpoint(s)

Analysis of secondary endpoints (6MWD, Borg dyspnea score, functional class, symptoms of PAH, CPET, PedsQL and cMRI parameters) will be descriptive in nature. The PedsQL questionnaire scores will be computed in accordance with the established scoring instructions. Numeric endpoints for post-Baseline assessments will be compared to Baseline using the appropriate statistical test, and p-values will be calculated for descriptive purposes; no formal hypothesis testing is planned.

Plasma samples will be analyzed for treprostinil using a validated bioanalytical plasma assay. Individual and mean treprostinil plasma concentration data and treprostinil pharmacokinetic parameters, such as peak observed plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), area under the plasma concentration-time curve ($AUC_{0\text{-}inf}$), will be determined as able and summarized using descriptive statistics.

10.3.3 Safety Analyses

All subjects who receive oral treprostinil (study drug) will be included in the safety population. Statistical summaries of safety data will be descriptive and exploratory in nature,

focusing on the incidence of adverse experiences. The safety data collected in this study will be presented in listings and summary tables.

Treatment-emergent changes in vital signs, ECG recordings, incidence of treatment-emergent AEs, and treatment-emergent changes in clinical laboratory parameters (i.e., hematology, clinical chemistry, and urinalysis) and physical examination will be evaluated.

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The incidence of AEs within each cohort will be presented in summary tables overall and by system organ class and preferred term.

Vital sign and clinical laboratory data collected prior to dosing will serve as Baseline values for evaluation of data collected during the treatment period. Summary statistics will be calculated for measured values at each time point assessed, as well as change from baseline values within each cohort.

No inferential statistical analyses are planned for safety data.

10.4 INTERIM ANALYSIS

A DSMB will be established for the study, composed of approximately two to three independent members including physicians knowledgeable in the treatment of PAH and pediatric PAH. Once five subjects have enrolled in Cohort 1 and transitioned from IV/SC Remodulin, the safety data will be reviewed by the DSMB. The IV/SC Remodulin dose will be between 25-75 ng/kg/min, inclusive, for the first five subjects enrolled in Cohort 1. Following the DSMB safety review, the dose range may be expanded to 25-125 ng/kg/min, inclusive, for the remaining subjects.

Additionally, if two or more of the first five subjects within any cohort meet the pre-specified stopping criteria, the data from that cohort will be reviewed prior to enrolling additional subjects into that cohort.

Analysis of pharmacokinetic samples may be performed, as warranted, to guide dosing.

10.5 OTHER ANALYSES

Additional exploratory analyses may be conducted based on available study data.

10.6 DATA LISTINGS AND SUMMARIES

The Safety population will be used for all data listings, summaries and figures. All available data will be presented with no imputation for any missing data. Subjects will contribute the data available up to the point of study completion, or study discontinuation for any reason.

In general, listings will be sorted by subject, descriptive summaries will include number of observations (n), mean, standard deviation (SD), median, minimum, maximum for continuous variables and n and percent for categorical variables. For all continuous variable summaries, n, arithmetic mean, median, minimum, maximum, SD, % coefficient of variation (CV), and 95% confidence interval (CI) for the arithmetic mean will be provided.

Plasma concentration data and derived pharmacokinetic parameters will be summarized and displayed in both tabular and graphical form. Noncompartmental analysis of concentration time data will be performed using WinNonlin. Comparative plots of individual concentration data will be produced separately for each cohort as well as summaries across subjects.

11 PACKAGING AND FORMULATION

11.1 CONTENTS OF STUDY DRUG

United Therapeutics will supply oral treprostinil extended release tablets for administration in the study. The tablets may be provided as 0.125, 0.25, 1, or 2.5 mg strengths. Tablets contain 0.125 mg treprostinil (equivalent to 0.15875 treprostinil diolamine), 0.25 mg treprostinil (equivalent to 0.3175 mg treprostinil diolamine), 1 mg of treprostinil (equivalent to 1.27 mg treprostinil diolamine) or 2.5 mg of treprostinil (equivalent to 3.175 mg treprostinil diolamine). Oral treprostinil will be provided in child resistant bottles each containing 100 tablets.

11.2 LABELING

Each bottle will be labeled in accordance with all applicable national regulations, to include at least the following information: oral treprostinil (study drug), strength, quantity, manufacture date, lot number, expiratory date, Sponsor name and address, protocol number, cautionary statements, and storage conditions.

11.3 STORAGE AND HANDLING OF CTM

Bottles of oral treprostinil should not be stored above 25˚C (77˚F) with excursions permitted up to 30˚C (86˚F). In addition, bottles should be stored in a secure, controlled location with appropriate temperature monitoring. Oral treprostinil should not be frozen or exposed to heat.

11.4 SUPPLY AND RETURN OF CTM

Study sites will be supplied with a sufficient quantity of oral treprostinil (study drug) to begin enrollment in the study. Appropriate arrangements will be made for resupply with respect to each subject's visit schedule. Additional oral treprostinil supply may occur between protocol-required visits as required.

Subjects/caregivers should be instructed to return all oral treprostinil, including empty bottles, to the appropriate study personnel on an ongoing basis at each study visit.

Unused oral treprostinil including both used and unused bottles 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.

11.5 DRUG ACCOUNTABILITY

The Investigator is responsible for oral treprostinil (study drug) accountability and reconciliation. The Investigator or his/her designee will be responsible for maintaining accurate records of the quantity and dates of all investigational product supplies received, and the amount administered to each subject. The quantity of any investigational product lost, missing, destroyed, etc. must also be accounted for and documented. At each subject visit,

site personnel should assess amount of drug dispensed, drug returned, and dosing information to confirm drug accountability and compliance.

12 REGULATORY AND ETHICAL OBLIGATION

12.1 U.S. 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 institutional research boards (IRBs) that require it. Any additional national reporting requirements as specified by the applicable regulations, regulatory authorities, or IRB will also be fulfilled during the conduct of the study.

12.2 INFORMED CONSENT AND ASSENT REQUIREMENTS

This study involves research in underage subjects. 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 and a legally authorized representative must sign and date an IRB-approved informed consent form prior to the conduct of any study-related activities. A copy of the signed consent form will be given to the legally authorized representative and the original will be retained in the study site's records. Assent to participate in the study will be obtained and documented in underage subjects, in accordance with the IRB policy for obtaining assent.

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 and provide the Sponsor with a copy of the approval letter. The IRB must also review and approve the study site's informed consent form 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 informed consent form and advertising materials must be forwarded to the Sponsor for review before submission to the IRB prior to the start of the study.

If, during the study, it is necessary to amend either the protocol or the informed consent form, the Investigator is responsible for obtaining IRB approval of these amended documents prior to implementation. Copies of the IRB 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 that require it.

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

12.4 PRESTUDY DOCUMENTATION REQUIREMENTS

Before the commencement of the clinical trial, the following documents will be provided to the site: Investigators' Brochure for oral treprostinil, protocol, model informed consent form, budget and clinical trial agreement template.

The site will be required to provide the following documents to United Therapeutics Corporation or designee prior to study start: Signature page of the protocol, Form FDA 1572, financial disclosure form, IRB composition and roster, IRB protocol and informed consent approval letters, curriculum vitae of study staff listed on the Form FDA 1572 and an executed clinical trial agreement.

12.5 SUBJECT CONFIDENTIALITY

Every effort will be made to keep medical information confidential. United Therapeutics Corporation and the agents of the Sponsor, the FDA or other regulatory bodies, and the IRB 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 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 prior to implementation.

A report documenting study termination must also be submitted to and acknowledged by the appropriate IRB 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 two 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 two 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 site and 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.

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15 APPENDICES

15.1 PROCEDURE FOR SIX-MINUTE WALK EXERCISE TEST AND DYSPNEA SCALE

General Procedures

The 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[1] and the usual practice of the investigative site.

The area used for the 6MWT should be pre-measured at approximately 30 meters in length and at least 2-3 meters in width. There should 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 patient 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" while simultaneously stopping the watch and then measure the distance walked.

Oxygen saturation and HR will be measured at rest prior to the 6MWT and monitored continuously during the walk. Oxygen saturation may be measured by fingertip or forehead monitor. Recovery monitoring (HR and oxygen saturation) will be performed and documented at minute 0 (immediately upon stopping the 6MWT), minute 1, minute 2 and minute 3 post-walk. Recovery monitoring must continue until the HR is within 10 beats of resting values and the oxygen saturation is within 2% of resting values or until at least 20 minutes of recovery monitoring has been performed and the Investigator considers the

[1] ATS Statement: Guidelines for the Six-Minute Walk Test. Am J Respir Crit Care Med 2002; 166: 111–117.

subject to be clinically stable. The Borg score will be assessed before and after the walk. The recovery monitoring may be terminated early with approval from the Investigator only.

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 from this point and follow the hallway to the marker (*e.g.*, chair) at the end, turn around and walk back. When you arrive back at the starting point you will go back and forth again. You will go back and forth as many times as you can in the 6-minute period. You may stop and rest if you need to. Just remain where you are until you can go on again. However, the most important thing about the test is that you cover as much ground as you possibly can during the six 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 when I say "GO."

The person administering the test will tell the subject the time at 2 and 4 minutes by saying:

> "You have completed 2 minutes."

And then by saying:

> "You have completed 4 minutes."

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

Dyspnea Score

Before and immediately after the walk, the person administering the test will obtain a rating of dyspnea using the 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 (indicate the scale). 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."

15.2 FUNCTIONAL CLASSIFICATION

PANAMA FUNCTIONAL CLASSIFICATION FOR CHILDREN AGED 5- 16 YEARS

Class	Children with pulmonary hypertension
I	Asymptomatic, growing along own centiles, attending school regularly, no limitation of physical activity, playing sports with his/her classmates
II	Slight limitation of physical activity, unduly dyspnoeic and fatigued when playing when playing with his/her class-mates. Comfortable at rest. Continues to grow along own centiles. School attendance 75% normal. No chest pain
IIIa	Marked limitation of physical activity. No attempt at sports. Comfortable at rest. Less than ordinary activity causes undue dyspnoea, fatigue, syncope or chest pain. Schooling compromised, <50% normal attendance
IIIb	Unable to attend school, but mobile at home and interacting with friends. Wheelchair needed outside the home. Growth compromised. Poor appetite. Supplemental feeding. Less than ordinary activity (dressing) causes undue dyspnoea, fatigue, syncope and/or presyncope or chest pain. Plus features of Class IIIa)
IV	Unable to carry out any physical activity without undue dyspnoea, fatigue, syncope or chest pain, unable to attend school, wheelchair dependant, not interacting with friends. Syncope and/or right heart failure. Plus features of Class III

WHO FUNCTIONAL CLASSIFICATION FOR PH

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

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

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

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

15.3 PEDIATRIC QUALITY OF LIFE INVENTORY (PEDSQL)

[redacted]

15.4 GUIDELINES AND DEFINITIONS FOR RECORDING ADVERSE EVENTS

The Principal Investigator or a designated member of his/her staff will probe each subject for any AEs that may have occurred. The Investigator should always ask the same question when conducting the verbal probe in order 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, this should be reported as an AE. The Investigator may repeat the diagnostic procedure or laboratory test or request additional tests to verify the results of the original tests. When possible, a diagnosis associated with the abnormality should be used as the reported AE.

Using provided definitions, the Investigator will then:

(1) rate the intensity and seriousness of the AE,
(2) estimate the causality of the AE to oral treprostinil (study drug), and
(3) note actions taken to counteract the AE.

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

INTENSITY

An assessment of the relative intensity (severity) of an AE is based on the Investigator's clinical judgment. 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 AE.

SERIOUSNESS

A serious AE 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 may be considered a serious AE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this 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 (e.g., hospitalization for a routine RHC).
- Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition (e.g., pre-planned operation which does not lead to further complications etc.).
- Treatment of an emergency, in an outpatient setting for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

CAUSALITY

An estimate of causality between a specified AE 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 the 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
  - Unlikely due to an alternative illness or external event (e.g. surgical procedure, accident)

- 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 study drug administration. Rechallenge (the original study drug dose was not restarted) is not required 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
  - Not readily explained by an intercurrent illness
  - Not readily explained by external event
  - Improves on discontinuation of study drug
  - If study drug had been discontinued, may recur on reintroduction of study drug

ACTION TAKEN

STUDY DRUG DOSE MODIFICATION*

- Dose Not Changed - the dose or regimen of the study drug was not changed.
- 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 AE was ongoing at the time of death or at the time the subject was lost to follow up.
- Recovered / Resolved - The AE resolved.
- Recovered / Resolved with Sequelae - The AE is considered resolved however there is a 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 AE is improving but is not yet completely recovered/resolved.
- Unknown - The outcome of the AE cannot be determined.

15.5 PHARMACOKINETIC SAMPLE PROCESSING

Collection, Processing and Shipment of Plasma Specimens

Cohort 1: A total of 8 approximately 3 mL blood specimens (approximately 24 mL) for PK analysis will be collected from each subject during the study. Pharmacokinetic samples will be collected at Baseline and Week 24.

Cohorts 2 and 3: A total of 5 approximately 3 mL blood specimens (approximately 15 mL) for PK analysis will be collected from each subject during the study. Pharmacokinetic samples will be collected at Week 24 only.

Pharmacokinetic Specimen Collection

Collection may occur by venipuncture or cannula with a saline lock; the use of heparin **is not** permitted.

Cohort 1: The Baseline PK sampling will begin with a time 0 sample and the following subsequent time points: 4 and 8 hours after time 0. At Baseline, time 0 should be at the same time of the day that it is estimated the Week 24 oral treprostinil (study drug) dose will occur.

All Cohorts: No oral treprostinil dose changes are allowed within five days of the Week 24 PK sampling, unless required to protect subject safety. All subjects on a TID dosing regimen will undergo the Week 24 PK assessment based on the first daily dose (morning dose) of oral treprostinil. If a subject is on a QID dosing regimen, the Investigator may conduct the PK assessment based on the first daily dose (morning dose) or the second daily dose (midday dose) at their discretion. The PK assessment dose of study drug at Week 24 should occur approximately 8 hours after the prior evening's last dose of oral treprostinil for subjects using the morning dose for the PK assessment. When using the midday dose for the PK assessment, the midday dose of study drug should occur 4 to 6 hours after that day's morning dose. The Week 24 PK sampling will begin with a pre-dose sample (immediately prior [i.e., 10 minutes ±5 minutes] to the administration of the PK assessment oral treprostinil [study drug] dose), and the following subsequent time points: 2, 4, 6, and 8 hours after the PK assessment dose

of study drug (all time points will be based off of the time the PK assessment dose of study drug is administered).

If the subject is on a TID regimen, no other doses of oral treprostinil should be taken during the PK sampling period; subjects should take their next dose of oral treprostinil (midday dose) after the final 8-hour PK sample is collected.

If the subject is on a QID regimen, the subject will take their next daily dose (midday dose or early evening [PM #1] based on timing of PK assessment dose) between the 4 and 6 hour time points of the PK sampling (±10 minutes) with food, based on the subjects typical dosing schedule.

Samples should be drawn within a ±10 minute window from their scheduled time point. Record the time and reason for late blood draws in the eCRF. Hemolyzed blood samples may be redrawn. Indicate hemolyzed sample in the eCRF.

Specimen Processing

- Collect approximately a 3 mL blood specimen in an evacuated glass tube containing **K_3-EDTA** as an anticoagulant and immediately place the specimen on ice.
- Within 1 hour of collection, centrifuge the specimen at 4 ºC for 10-15 minutes at 3000 g.
- Label the shipping tube with the subject number, treatment, and specimen collection time and date.
- Pipette approximately 1 mL plasma into a shipping tube. Pipette the remainder of the plasma into a second, identically labeled tube for use as a backup specimen.
- Freeze samples immediately at -20 to -25ºC. The 1 mL sample will be transported on dry ice to the Sponsor-designated laboratory for analysis. The remainder sample will be retained at the site and transported later in the event of an emergency or if deemed necessary by the Sponsor.

Shipping Procedures

- All shipments must be accompanied by a packing list. Please note on the packing list any specimens that are hemolyzed.
- Package the shipping tubes to prevent breakage and contamination in Styrofoam boxes containing a generous supply of dry ice that will allow for 3 days in transit.
- Prior to the shipment of specimens, contact the Sponsor and the bioanalytical laboratory by phone and fax or email. An advanced electronic copy of the packing list should also be provided to the laboratory.
- Samples should be shipped overnight to the bioanalytical laboratory, on dry ice, on a Monday, Tuesday, or Wednesday.