Intravenous Remodulin (Treprostinil) as Add-on Therapy for the Treatment of Persistent Pulmonary Hypertension of the Newborn: A Randomized, Placebo-Controlled, Safety and Efficacy Study

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CONFIDENTIAL

UNITED THERAPEUTICS CORPORATION

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Amendment 1:	FINAL 29 Aug 2014
Amendment 2:	FINAL 30 Oct 2015
Amendment 3:	FINAL 15 Apr 2016

LIST OF CONTACTS FOR STUDY

Study Sponsor	United Therapeutics Corp. 55 TW Alexander Drive Research Triangle Park, NC, USA 27709

INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "Intravenous Remodulin (treprostinil) as Add-on Therapy for the Treatment of Persistent Pulmonary Hypertension of the Newborn: A Randomized, Placebo-Controlled, Safety and Efficacy Study," Amendment 3 dated 15 Apr 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, Declaration of Helsinki, 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 have read the current Clinical Investigators' Brochure for Treprostinil for Injection and acknowledge that review of the information contained in the Clinical Investigators' Brochure is a requirement for Investigators before using treprostinil in this clinical trial.

This protocol has been received for information only and must not be implemented before all necessary regulatory agency and ethics approval documents have been obtained.

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

PROTOCOL SYNOPSIS

Title	Intravenous Remodulin (treprostinil) as Add-on Therapy for the Treatment of Persistent Pulmonary Hypertension of the Newborn: A Randomized, Placebo-Controlled, Safety and Efficacy Study
Study Phase	Phase II
Indication	Persistent Pulmonary Hypertension of the Newborn (PPHN)
Primary Objective	To explore the safety and treatment effect of intravenous (IV) Remodulin as add on therapy in neonates with PPHN compared to placebo. Efficacy will be assessed by a composite endpoint of clinical worsening through Day 14 as defined by one of the following: • Death • Initiation of extracorporeal mechanical oxygenation (ECMO) per institutional policies • Need for additional treatment (initiation of an additional targeted pulmonary vasodilator therapy [e.g., phosphodiesterase-5 inhibitor [PDE-5i], endothelin receptor antagonist [ERA], prostanoid, L-citrulline])
Secondary Objectives	To assess the effect of IV Remodulin as add on therapy in neonates with PPHN compared to placebo in the following: • Change in Oxygenation Index (OI) from Baseline to Hours 12, 24, 72, Days 7 and 14 and/or prior to study drug discontinuation/weaning • Change in PaO_2 /FiO_2 (P/F ratio) from Baseline to Hours 12, 24, 72 • Change in pre- and post-ductal oxygen saturation (SpO_2) from Baseline to Hours 6, 12, 24 and 72 • Time to discontinuation of inhaled nitric oxide (iNO) • Time on mechanical ventilation • Time to initiation of ECMO • Time to clinical worsening • Change in N-terminal pro-Brain Naturetic Peptide (NT-proBNP) • Safety (adverse events (AEs), clinical laboratories, and physical exam findings) To evaluate treprostinil pharmacokinetics in neonates with PPHN
Study Design	Randomized, double-blind, placebo-controlled, multi-center, comparative study
Sample Size	The study may enroll approximately 70 subjects to ensure at least 66 evaluable subjects; no more than 32 evaluable subjects with a diagnosis of PPHN associated with congenital diaphragmatic hernia (CDH) will be enrolled.

Summary of Subject Eligibility Criteria	Eligible subjects will be at least 34 weeks gestational age, 2 kg at screening and have a diagnosis of PPHN. The subject must have two consecutive OIs of 15 or greater, separated by at least 30 minutes, after having received iNO for at least 3 hours prior to randomization and initiation of study drug.
Drug Dosage and Formulation	Study drug (Remodulin or matching placebo) will be supplied in 20mL clear glass vials containing 1mg/mL treprostinil or placebo. Each vial must be discarded within 30 days after first opening. A new vial should be used for each subject. Study drug must be diluted with high-pH glycine diluent (Sterile Diluent for Remodulin, Sterile Diluent for Flolan, or Sterile Diluent for Epoprostenol Sodium), Sterile Water for Injection, or 0.9% Sodium Chloride Injection, prior to administration as a continuous intravenous infusion via an indwelling central venous catheter, using an infusion pump designed for intravenous drug delivery. If clinically necessary, a peripheral intravenous cannula may be used for short term administration of study drug. A dedicated IV line or port/lumen is required for the IV administration of study drug. In the event dedicated central venous access cannot be established, or in the opinion of the Investigator the patient is too unstable to attempt to establish a dedicated central venous access line for IV administration of study drug, study drug may be initiated as a continuous subcutaneous (SC) infusion at the discretion of the Investigator. Subjects initiated on IV administration of study drug who lose venous access may be transitioned to SC administration. Dilution of study drug is usually not required for continuous SC administration in an adult population; however, based upon the selected SC infusion pump flow rate capabilities, the subject's dose weight, and dose in this neonate patient population, dilution will likely be required for SC administration (especially for smaller babies and lower doses, or during weaning of study drug). If dilution is required for SC administration, Sterile Water for Injection or 0.9% Sodium Chloride for Injection should be used. The line should not be flushed to avoid an accidental over dosage. ***Initiating study drug*** Study drug will be initiated at 1ng/kg/min. The dose of study drug should be increased by up to 2ng/kg/min every 2 hours as tolerated and clinically indicated by the physician. As some subcutaneous infusion pumps may not accommodate a starting dose of exactly 1ng/kg/min, the site may proceed with a starting dose as close to 1ng/kg/min as possible. The initial starting dose should not exceed 2ng/kg/min and should be increased by approximately 1-2ng/kg/min every 2 hours as tolerated and clinically indicated by the physician.

Dose titration

The dose escalation should continue in up to 2ng/kg/min increments every 2 hours, as tolerated and clinically indicated by the physician, while the OI is ≥15 (or the FiO_2 requirement is ≥60%, if the OI is not calculated) in the absence of dose-limiting adverse events (e.g., due to systemic hypotension). When the OI is between 10-14 and the study drug dose is ≤10ng/kg/min, the dose should continue to be increased; if the study drug dose is >10ng/kg/min and the OI is between 10-14, any further dose escalation will be left to the discretion of the clinicians/investigator according to the clinical condition of the subject, and the perceived need for additional pulmonary vasodilation.

The dosing of study drug is based upon the OI (as long as it is calculated) and then by the FiO_2 as needed. Suggested dose titration parameters are listed in the table below.

OI	**FiO_2** ***(To be used when OI is not calculable)***	**Dosing Strategy**
≥15	≥60%	Dose increase, as tolerated
10-14	--	*Current Remodulin dose >10ng/kg/min* Hold dose or dose increase if clinical condition warrants further pulmonary vasodilation.
10-14	--	*Current Remodulin dose ≤10ng/kg/min* Dose increase, as tolerated
<10	<60%	Begin weaning. The iNO should be weaned and discontinued prior to initiating weaning of study drug.

Dose maintenance

Once the target therapeutic goal has been reached (i.e., OI <10 or FiO_2 <60%) the current dose of study drug should continue for at least 12 hours prior to beginning to wean study drug.

Dose Wean

Down titration will begin once the subject is no longer receiving iNO and the OI is <10 (or the FiO_2 is <60% if the OI is not calculated); iNO should be weaned and discontinued prior to initiating weaning of study drug.

It is recommended the dose of study drug be decreased by no more than 10ng/kg/min per day (in divided increments, either in the same manner as the dose was increased or as determined by the Investigator). Faster weaning may occur if required per subject care.

	Subjects who have residual or chronic pulmonary hypertension that does not fully resolve by Day 14 may continue to receive study drug for up to an additional 14 days (for a total of up to 28 days) per the Investigator's discretion, if clinically indicated.
Control Group	Placebo
Route of Administration	Continuous intravenous infusion; administration as a continuous subcutaneous infusion may be used in subjects in whom dedicated central venous access cannot be established, who are too unstable to attempt to establish a dedicated central venous access line for IV administration of study drug, or for subjects initiated on an IV infusion of study drug who lose venous access.
Procedures	Once parental or legal guardian consent has been provided, the subject will undergo the appropriate screening procedures to determine eligibility. After the inclusion/exclusion criteria have been confirmed, the subject will be enrolled and randomized via the IWRS. ***Study drug initiation and administration phase*** • First 72 hours o Vital signs and OI assessments will occur approximately every six hours (6 ± 2 hours) while on study drug. o BP, HR and SpO_2, and doses of inotropes will also be collected with each study drug dose change. o Physical examination and NT-proBNP will be collected daily for the first 72 hours. o After 24 hours (+6 hours) on study drug, one blood sample will be collected for pharmacokinetic (PK) analysis. • Day 4 throughout duration of study drug treatment o Assessments will occur at least once daily including vital signs, FiO_2, blood gasses, and OI assessment. o BP, HR, SpO_2 and doses of inotropes will also be collected with each study drug dose change. • Day 7 and Day 14 o In addition to the daily assessments, physical examination, clinical laboratory assessments, echocardiogram, and NT-proBNP will be performed. ***Study drug weaning and discontinuation*** • Immediately prior to weaning study drug o Key assessments include physical examination, vital signs, clinical laboratory assessments, echocardiogram, OI assessment, FiO_2, NT-proBNP, inotrope support, and PK sample collection.

- Every 24 hours while weaning
  - Assessments will occur once each day while weaning study drug and include vital signs, physical examination, FiO_2, and mean airway pressure (MAP) if still on mechanical ventilation.
  - BP, HR, SpO_2, FiO_2, and doses of inotropes will also be collected with each study drug dose change.

Follow-up

- Within 12 hours after last dose of study drug
  - Physical examination, vitals, FiO_2, blood gasses, MAP, clinical laboratory assessments, and NT-proBNP
- 48 hours after the last dose of study drug
  - Vitals, clinical laboratory assessments, and echocardiogram
- Post-treatment data will be collected until subject is withdrawn from the study, death, time of hospital discharge, or until 4 weeks after last dose of study drug, whichever comes first.
  - The following key assessments will occur at time of withdrawal from study, hospital discharge, or at 4 weeks after last dose of study drug, whichever comes first: physical exam, vital signs, and clinical laboratory assessments.
  - Additionally, time on mechanical ventilation, time on inhaled iNO, and time of initiation of EMCO (if applicable) will be recorded.
  - The subject's participation in the study will conclude at the time of hospital discharge, death, withdrawal from the study, or at 4 weeks after last dose of study drug, whichever comes first.
    - Subjects with ongoing AEs at the time of study withdrawal or hospital discharge will continue to be followed for their AEs until either resolution (or return to normal or Baseline values), until judged by the Investigator to no longer be clinically significant, or until 4 weeks after last dose of study drug. All SAEs will be followed until resolution, death, or the subject is lost to follow-up, even if they are ongoing more than 4 weeks after the last dose of study drug.

Statistical Considerations	Based on the systematic review of use of nitric oxide for respiratory failure in infants by Finer and Barrington, 57.9% (194/335) subjects in the control group had an outcome of death or requirement for EMCO. In this study, assuming 60% subjects in placebo group and 30% subjects in Remodulin group with an outcome of death, requirement for EMCO, or need for additional PAH therapy, we calculated that 66 subjects (33 subjects per treatment group) will have at least 80% power to show a significant difference in favor of Remodulin at alpha level of 0.05 (one-sided test).

	Approximately seventy subjects are planned to be randomized (1:1) to either receive treatment with Remodulin or placebo on top of the standard of care.
Sponsor	United Therapeutics Corp. 55 TW Alexander Dr PO Box 14186 Research Triangle Park, NC, USA 27709

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LIST OF ABBREVIATIONS

ABG	Arterial blood gas
ADP	Adenosine diphosphate
AE	Adverse event
ALT	Alanine transaminase
ASD	Atrial septal defect
AST	Aspartate transaminase
BP	Blood pressure
BUN	Blood urea nitrogen
°C	Degree Celsius
cAMP	Cyclic adenosine monophosphate
CBG	Capillary blood gas
CDH	Congenital diaphragmatic hernia
CHD	Congenital heart disease
CI	Confidence interval
CO_2	Carbon dioxide
CV	Coefficient of variation
CYP	Cytochrome
DSMB	Data safety monitoring board
ECHO	Echocardiogram
ECMO	Extracorporeal membrane oxygenation
EC	Ethics Committee
eCRF	Electronic case report form
EMA	European Medicines Agency
ERA	Endothelin receptor antagonist
°F	Fahrenheit
FDA	Food and Drug Administration
FiO_2	Fraction of inspired oxygen
GCP	Good Clinical Practice
HCO_3	Bicarbonate
HR	Heart rate
ICH	International Conference on Harmonisation
ICU	Intensive care unit
IND	Investigational new drug
iNO	Inhaled nitric oxide
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive web response system
kg	Kilogram
LFTs	Liver function tests
MAP	Mean airway pressure
MAS	Meconium aspiration syndrome

min	Minute
mg	Milligram
mmHg	Millimeters mercury
mL	Milliliter
n	Number
ng	Nanogram
NICU	Neonatal intensive-care unit
NO-cGMP	Nitric oxide cyclic guanosine monophosphate
NT-proBNP	N-terminal pro-Brain Naturetic Peptide
OI	Oxygenation index
P/F	Ratio of arterial oxygen concentration to the fraction of inspired oxygen (PaO_2/FiO_2)
PA	Pulmonary artery
$PaCO_2$	Partial pressure of arterial carbon dioxide
PAH	Pulmonary arterial hypertension
PaO_2	Partial pressure of arterial oxygen
PCVC	Percutaneous central venous catheter
PDA	Patent ductus arteriosus
PDE-5i	Phosphodiesterase type-5 inhibitor
PFO	Patent foramen ovale
PGI_2	Prostacyclin
PH	Pulmonary hypertension
PICC	Peripherally inserted central catheter
PK	Pharmacokinetic
PPHN	Persistent pulmonary hypertension of the newborn
PR	Pulmonary regurgitation
$PvCO_2$	Partial pressure of venous carbon dioxide
PvO_2	Partial pressure of venous oxygen
RDS	Respiratory distress syndrome
RR	Respiratory rate
RV	Right ventricle
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SpO_2	Saturation of peripheral oxygen
SvO_2	Mixed venous oxygen saturation
Temp	Temperature
TR	Tricuspid regurgitation
US	United States
UVC	Umbilical venous catheter
VBG	Venous blood gas
VSD	Ventricular septal defect
µL	Microliter

1 BACKGROUND AND RATIONALE

1.1 DEFINITION OF CLINICAL PROBLEM

As part of the normal birth transition, the pulmonary vascular resistance decreases as the lungs expand and the ductus arteriosus closes. Persistent pulmonary hypertension of the newborn (PPHN) is the failure of the pulmonary vasculature to make this transition leading to diminished cardiac output and obligatory right to left shunting. The incidence of PPHN has been estimated at 1.9/1000 live births with reported mortality ranging from 4-33% (1). PPHN can be characterized as one of three types: abnormally constricted pulmonary vasculature due to lung parenchymal diseases (e.g., meconium aspiration syndrome [MAS], respiratory distress syndrome [RDS] or pneumonia); normal lung parenchyma with remodeled pulmonary vasculature (idiopathic PPHN) or hypoplastic vasculature as seen in congenital diaphragmatic hernia [CDH]) (2).

Management of PPHN is aimed at optimization of cardiac and lung function and reducing pulmonary vascular resistance. This may include: mechanical ventilation, sedation, neuromuscular blockade, inotropic support, intravenous volume replacement, pulmonary vasodilator therapy, inhaled nitric oxide, or therapy with phosphodiesterase-5 inhibitors (PDE-5i) or endothelial receptor antagonists (ERA), and in severe cases, mechanical support with extracorporeal membrane oxygenation (ECMO).

Currently, inhaled nitric oxide (iNO) is the only treatment for PPHN approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). Inhaled nitric oxide was studied in two double-blind, placebo-controlled trials which enrolled neonates with hypoxic respiratory failure. The objectives of these studies were to determine whether iNO would reduce the occurrence of death and/or initiation of ECMO in neonates with hypoxic respiratory failure. In these trials, hypoxic respiratory failure was caused by MAS, pneumonia/sepsis, idiopathic PPHN, and RDS. Both studies demonstrated that iNO reduced the need for ECMO in this population; however there was no difference in mortality in either study. Neither of these trials included subjects with CDH. Across these studies, approximately 30-40% of neonates did not respond to iNO (defined as a change from baseline in partial pressure of oxygen in arterial blood (PaO_2) of $\leq$10 mmHg) (3,4). In clinical

practice, critically ill neonates unresponsive to iNO will typically receive ECMO; however, an alternative option could include the addition of another pulmonary vasodilator in an effort to reduce the pulmonary vascular resistance.

1.2 REMODULIN (TREPROSTINIL) BACKGROUND

Treprostinil is a chemically stable tricyclic analogue of prostacyclin (PGI_2), which is approved for the treatment of pulmonary arterial hypertension (PAH) in the US, EU, and many other countries under the brand name Remodulin. The pharmacology of treprostinil has been extensively characterized for the treatment of PAH using either a subcutaneous (SC) or intravenous (IV) continuous infusion. A detailed description of preclinical and clinical information of treprostinil for injection is provided in the Investigator's Brochure.

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

The efficacy of Remodulin in adult patients with PAH has been established in both the IV and SC routes (5-7). However, there is a growing body of literature to support the use of Remodulin in the pediatric population. Multiple published reports of the use of chronic Remodulin in children as young as 20 weeks of age have been reported without unexpected adverse events (AEs) (8-10). Acute dosing of SC and IV Remodulin has been used in children as young as 6-8 weeks, including a case report published regarding the use of IV

Remodulin in a neonate for the treatment of PPHN (11-13). In this case study, the subject was initiated at a dose of 1ng/kg/min of IV Remodulin and was titrated to a dose of 4ng/kg/min. Clinical response was noted within four days of initiation and down titration began after 10 days on therapy (11).

In children and adults, the most frequent AEs reported with Remodulin were related to the known pharmacological properties of treprostinil. These prostacyclin-related AEs are typically due to systemic effects that are characteristic of the prostacyclin class of medications (e.g., diarrhea, headache, nausea). To date, well over 10,000 patients, which includes over 1,000 pediatric patients (<12 years of age) and study subjects have been exposed to Remodulin for more than 11 years.

1.3 RATIONALE FOR DEVELOPMENT OF STUDY DRUG IN DISEASE / CONDITION

The pathophysiology of PPHN includes disruptions in the nitric oxide cyclic guanosine monophosphate (NO-cGMP), prostacyclin-cyclic adenosine monophosphate (cAMP), and endothelin signaling pathways. Prostacyclin appears to increase during late gestation suggesting its importance in the cardiopulmonary transition of newborns. An imbalance in the biosynthesis of prostacyclin and synthesis of the constrictor thromboxane A_2 has been identified to occur in pulmonary arterial hypertension, and similar imbalances in vasoactive and vasoconstrictive mediators has been observed in studies of fetal pulmonary hypertension (14,15). Current standard of care treatment for PPHN is iNO; however, approximately 40% of patients do not fully respond to iNO (2,3). Treprostinil, a prostacyclin analogue, may work in synergy with iNO for the treatment of PPHN to enhance smooth muscle relaxation of the pulmonary vasculature. Treprostinil may also decrease the inflammatory response and improve pulmonary vascular remodeling in these patients.

1.4 CLINICAL HYPOTHESIS

This study aims to assess the safety and treatment effect of IV Remodulin as add-on therapy in neonatal subjects with PPHN as compared to placebo. This study will enroll subjects with PPHN who do not show an adequate response to iNO (defined as an oxygenation index [OI] of 15 or greater after three hours of iNO therapy) with the hypothesis that the addition of

Remodulin will reduce the rate of clinical worsening defined as death, the need for ECMO, or the need for additional pulmonary vasodilator therapy as compared to placebo. Additionally, this study aims to evaluate the dosing and pharmacokinetics of Remodulin in the neonatal population.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

To explore the safety and treatment effect of IV Remodulin as add on therapy in neonates with PPHN compared to placebo. Efficacy will be assessed by a composite endpoint of clinical worsening through Day 14 as defined by one of the following:

- Death
- Initiation of ECMO per institutional policies
- Need for additional treatment (initiation of an additional targeted pulmonary vasodilator therapy [e.g., phosphodiesterase-5 inhibitor [PDE-5i], endothelin receptor antagonist [ERA], prostanoid, L-citrulline]; refer to Section 3.3.1.1.1).

2.2 SECONDARY OBJECTIVES

To assess the effect of IV Remodulin as add on therapy in neonates with PPHN compared to placebo in the following:

- Change in OI from Baseline to Hours 12, 24, 72, Days 7 and 14 and/or prior to study drug discontinuation/weaning
- Change in PaO_2 /FiO_2 (P/F ratio) from Baseline to Hours 12, 24, 72
- Change in pre and post-ductal oxygen saturation (SpO_2) from Baseline to Hours 6, 12, 24 and 72
- Time to discontinuation of iNO
- Time on mechanical ventilation
- Time to initiation of ECMO
- Time to clinical worsening
- Change in N-terminal pro-Brain Naturetic Peptide (NT-proBNP)
- Safety (AEs, clinical laboratories, and physical examination findings)

To evaluate treprostinil pharmacokinetics in neonates with PPHN.

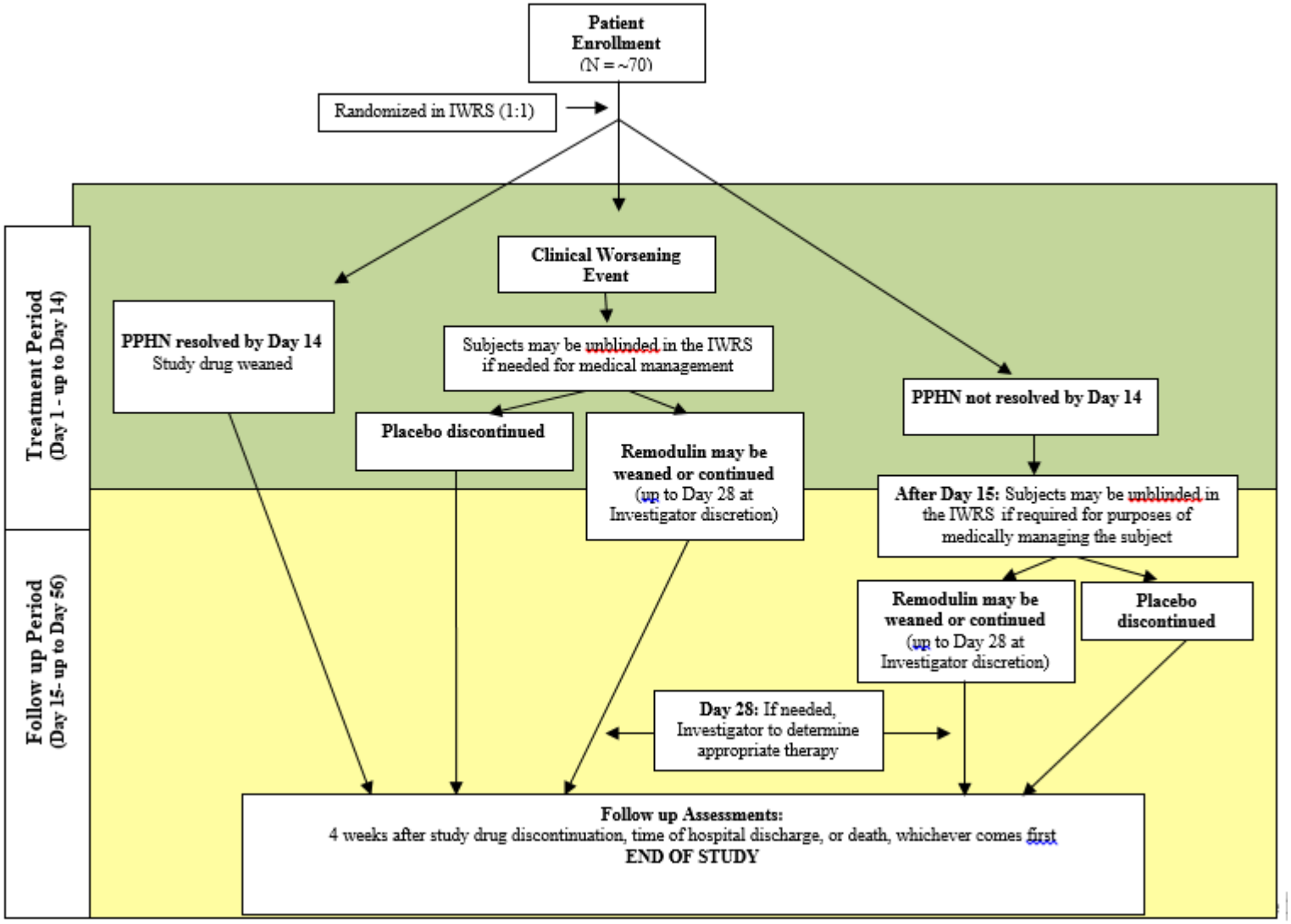
3 EXPERIMENTAL PLAN

3.1 STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, multi-center, comparative study that will enroll neonates in the intensive care unit (ICU) with PPHN. Eligible subjects must have two consecutive OIs of 15 or greater, separated by at least 30 minutes, after having received iNO for at least 3 hours. Once enrolled, subjects will be randomized to receive Remodulin (treprostinil) or placebo.

This study is designed to evaluate the treatment effect of Remodulin as add-on therapy compared to placebo during a 14-day treatment period. However, to assess continued safety in this neonatal population, subjects with residual or chronic pulmonary hypertension that does not fully resolve within 14 days may continue to receive study drug for up to an additional 14 days (up to 28 days total) per the Investigator's discretion. Post-treatment data will be collected until death, time of hospital discharge, time of withdrawal from study, or for 4 weeks after last dose of study drug, whichever comes first. Subjects with ongoing AEs at the time of hospital discharge will continue to be followed for their AEs until either resolution (or return to normal or Baseline values), until judged by the Investigator to no longer be clinically significant, or until 4 weeks after last dose of study drug. All SAEs should be followed until resolution, death, or the subject is lost to follow-up, even if they are ongoing more than 4 weeks after last dose of study drug.

Figure 3-1 Design Schematic



3.2 OVERALL SCHEDULE OF TIMES AND EVENTS

No procedures specifically for purposes of this study should be performed before a parent or legal guardian has provided written informed consent. All study-related events and activities including specific instructions, procedures, concomitant medications, and descriptions of AEs should be recorded in the appropriate source documents and electronic case report forms (eCRFs). Table 3-1 displays the overall schedule of events.

Table 3-1 Schedule of Events

		Study Drug Initiation and Administration					Study Drug Discontinuation				Follow-up/Final Assessments
Procedures	**Screening**	**Baseline[a]**	**First 72 hours of treatment**	**Day 4 throughout duration of study drug treatment[b]**	**Day 7 and Day 14[b]**	**Dose Changes**	**Immediately Prior to Study Drug Weaning or Discontinuation[k]**	**Every 24 hrs While Weaning [p]**	**Study Drug Discontinuation (within 12 hours)[q]**	**48 hrs after Study Drug Discontinuation[q]**	**Hospital discharge (after Day 14) / 4 weeks after Study Drug Discontinuation[b,c]**
Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Randomization		X									
Maternal History	X										
Physical Examination	X	X	X(daily)		X^{b}		X^{k}	X	X		X
Vital Signs[d]	X	X	$X^{d,o}$(q6 hrs)	X^{b}(daily)	X^{b}	X^{d}	X^{k}	X	X	X	X
OI Assessment[e]	X	X	$X^{e,o}$(q6 hrs)	$X^{b,e}$(daily)	$X^{b,e}$		$X^{e,k}$				
FiO_2	X	X	X^{o}(q6 hrs)	X^{b}(daily)	X	X	X^{k}	X	X		
Mean Airway Pressure[f]	X	X	$X^{e,o}$(q6 hrs)	$X^{b,e}$ (daily)	X		$X^{e,k}$	X	X^{e}		
Blood Gas/Lactate[g]	X	X	$X^{e,o}$(q6 hrs)	$X^{b,e}$ (daily)	X^{b}		$X^{e,k}$		X^{e}		
Clinical Laboratories[h]		X			X^{b}		X^{k}		X	X	X
NT-proBNP		X	X(daily)		X^{b}		X^{k}		X		
Echocardiogram[i]	X				X^{b}		X^{k}			X	
Clinical Worsening[j]		X---	---X---	---X(through Day 14)	X						
Pharmacokinetic Sample collection			X^{l} (collected after 24 hrs of treatment)				X^{k}				
Concomitant Medications[m]	X	X---	---X---	---X---		---X---	---X---	---X---	---X---	---X	
Record Doses of Inotropes/		X				X	X	X	X	X	
Adverse Events[n]	X	X---	---X---	---X---		---X---	---X^{n}---	---X---	---X---	---X---	---X^{n}

[a]Screening assessments can be used as Baseline values if they are conducted within 3 hours of randomization. Length and weight will only be assessed at Baseline. All doses of study drug will be calculated using Baseline weight. Study drug initiation is Hour 0 on the first day of treatment.

[b] The Day 4 and the 72 hour time point assessment will fall on the same calendar day. A separate set of assessments should be captured for the Day 4 assessment. Day 7 and Day 14 assessments should be performed even if the subject has discontinued study drug. If subjects are discharged from the hospital prior to study Day 14, Day 14 assessments should be completed prior to hospital discharge. Subjects may receive up to 28 days of study drug.

[c]Hospital discharge or 4 weeks after discontinuation of study drug (whichever comes first).

[d]Vital signs include BP, HR, RR, temperature, and SpO_2. SpO_2 will be collected both pre- and post-ductal for the first 72 hours. BP, HR, and SpO_2 will be collected with each study drug dose change.

[e] OI will be calculated as long as the subject is on mechanical ventilation and arterial blood gasses (ABGs) are collected.

[f] Collected for as long as the subject is on mechanical ventilation.

[g]ABGs will be collected as long as the subject has arterial access. Venous or capillary blood gas will be collected thereafter. Lactate will be drawn with each blood gas.

[h] Clinical labs include: chemistries, hematology, and liver function tests. Performed by institutional laboratory.

[I] If subject had historic ECHO performed within 36 hours prior to time informed consent was signed, then ECHO does not need to be repeated at Screening. A ±2 day window for Day 7 and Day 14 ECHO.

[j]Clinical worsening is assessed from Baseline to the conclusion of Day 14 or hospital discharge, whichever comes first. Events occurring after Day 14 will not count towards the primary analysis of clinical worsening.

[k]"Prior to wean" assessments will be collected after the dose has been maintained for at least 12 hours and no more than 1 hour prior to beginning to wean study drug. Assessments should be collected for subjects randomized to placebo; PK sample not required in subjects randomized to placebo. In the event that the subject will continue to receive Remodulin beyond Day 28, prior to wean assessments should take place on Day 28.

[l]A single PK sample will be collected after 24+6 hours of study drug dosing. The dose should have been maintained for at least 2 hours prior to the sample collection time.

[m]Concomitant medications will be captured up to 48 hours after the subject has stopped receiving study drug.

[n]Documentation of AEs will be recorded from the time informed consent is provided until subject is withdrawn from study, time of hospital discharge, or for 4 weeks after last dose of study drug, whichever comes first. All SAEs should be followed until resolution, death, or the subject is lost to follow-up, even if they are ongoing more than 4 weeks after completion of the subject's last dose of study drug/final visit. If the subject receives Remodulin after hospital discharge, beyond Day 56/End of study, or following withdrawal from the study, AEs/SAEs will be subject to AE/SAE reporting under local government post-marketing AE/SAE reporting requirements.

[o]Approximately every 6 hours (± 2 hours).

[p]Not required for subjects unblinded and identified on placebo, or subjects continuing on Remodulin beyond Day 28.

[q]In the event that study drug is not discontinued (i.e., the subject continues on Remodulin beyond Day 28), the "Study Drug Discontinuation" and "48 Hour after Study Drug Discontinuation" assessments will not be collected. Follow-up/End of Study assessments will be performed.

3.3 CLINICAL ASSESSMENTS

3.3.1 Efficacy

3.3.1.1 Assessment of Clinical Worsening

Efficacy will be assessed by a composite primary endpoint of clinical worsening assessed at Day 14 or hospital discharge, whichever comes first, as defined by one of the following events:

- Death
- Initiation of ECMO per institutional policies
- Need for additional treatment (initiation of additional targeted pulmonary vasodilator therapy for PPHN)

Clinical worsening will be evaluated from Baseline (initiation of study drug) to the time of discontinuation of study drug, discharge from the hospital, or at the conclusion of Day 14, whichever comes first. Events occurring after the first 14 days of treatment will not count towards the primary endpoint.

3.3.1.1.1 Need for Additional Treatment

The following criteria should be met prior to initiation of additional targeted pulmonary vasodilator therapy for PPHN (all criteria required):

- OI measurement >20
- In the clinical judgment of the Investigator, subject requires addition of another targeted pulmonary vasodilator therapy (e.g., PDE-5i, ERA, alternate prostanoid [epoprostenol, iloprost], L-citrulline) due to worsening of clinical status or unsatisfactory clinical response
- Subject has received study drug for at least 24 hours and reached a minimum dose of 10ng/kg/min, or is unable to tolerate further increases (e.g., due to systemic hypotension); ***OR***
    - If less than 24 hours, subject has two consecutive OI measurements >30 separated by at least one hour ***OR*** two consecutive arterial lactate levels of ≥4mmol/L separated by at least one hour

If an additional pulmonary vasodilator therapy is added after Day 14, the subject will not meet the primary endpoint definition of clinical worsening.

3.3.1.1.2 Extracorporeal Mechanical Oxygenation (ECMO)

ECMO will be initiated per institutional policy. Any subject who initiates on ECMO during the first 14 days of the study will meet the definition of clinical worsening. The initiation of ECMO after Day 14 will not be considered a clinical worsening event for the purposes of the primary endpoint of the study.

3.3.1.1.3 Death

Any subject who dies within the first 14 days of the study will meet the definition of clinical worsening. Deaths that occur after Day 14 will not be considered a clinical worsening event for the purposes of the primary endpoint of the study.

All deaths will be reported as a serious adverse event (SAE) (Section 9).

3.3.1.2 Oxygenation Index (OI)

The OI is an assessment of how much oxygen diffuses across the membranes of the lungs and into the blood when a subject inhales. Higher OIs indicate an increased risk of poor subject outcomes because the subject is unable to get as much oxygen out of each breath. Typically when the OI is greater than 40, ECMO is considered. The OI is calculated as follows:

$$OI = [MAP(mmHg) \times FiO_2(\%) / PaO_2(mmHg)] \times 100$$

An OI will be calculated at Screening, Baseline, approximately every 6 hours for the first 72 hours, daily starting on the fourth day of study drug for as long as the subject is on study drug, and within 1 hour prior to weaning study drug for as long as the subject has arterial access for collection of arterial blood gases (ABGs) and is on mechanical ventilation (Table 3-1). An OI will be collected on study Day 7 and Day 14 (as long as the subject has arterial access for collection of ABGs and is on mechanical ventilation) regardless if the subject has already been weaned from study drug.

The OI should be used to guide study drug dosing. When the OI cannot be calculated (i.e., no arterial access for ABGs and/or subject not on mechanical ventilation), FiO_2 will be used to guide dosing (per Section 6.1.3).

3.3.1.3 Mean Airway Pressure (MAP)

The MAP is the mean pressure applied during positive-pressure mechanical ventilation (standard or high frequency) and will be recorded while the subject is mechanically ventilated at Screening, Baseline, approximately every 6 hours for the first 72 hours, daily starting on the fourth day of study drug for as long as the subject is on study drug, within 1 hour prior to weaning/discontinuing study drug, every 24 hours while weaning, and at the time of discontinuation of study drug. The MAP will be recorded on study Day 7 and Day 14 (as long as the subject is on mechanical ventilation) regardless if the subject has already been weaned from study drug.

3.3.1.4 Fraction of Inspired Oxygen (FiO_2)

The FiO_2 and route of delivery will be assessed at Screening, Baseline, every 6 hours for the first 72 hours, daily starting on the fourth day of study drug for as long as the subject is on study drug, within 1 hour prior to weaning/discontinuing study drug, every 24 hours while weaning, and at the time of discontinuation of study drug. The FiO_2 and route of delivery will be recorded on study Day 7 and Day 14 regardless if the subject has already been weaned from study drug. Additionally, FiO_2 will be collected with each study drug dose change.

When OI is no longer calculated (i.e., no arterial access for ABGs), FiO_2 will be used to guide study drug dosing. The dose of study drug should be increased in the absence of dose-limiting AEs (e.g., hypotension) if the FiO_2 is ≥60%. When the FiO_2 is less than 60%, weaning of study drug can begin (see Section 6.1.4).

3.3.1.5 Blood Gas and Lactate

Blood gas (arterial, capillary, or venous) values will be collected at Screening, Baseline, every 6 hours for the first 72 hours, then daily starting on the fourth day of study drug for as long as the subject is on study drug. Additionally, blood gases will be assessed within 1 hour prior to weaning and at the time of study drug discontinuation. Blood gases will be assessed on study Day 7 and Day 14 regardless if the subject has already been weaned from study drug.

The ABGs should be collected from a post-ductal artery when possible. If a post-ductal arterial catheter is not available, it should be noted in the eCRF that the ABG was collected from a pre-

ductal artery. The ABGs will include: PaO_2, partial pressure of arterial carbon dioxide ($PaCO_2$), bicarbonate (HCO_3), oxygen saturation (SaO_2), and pH.

Capillary or venous blood gasses (CBGs or VBGs) will be collected when the subject no longer has arterial access. The CBG or VBGs will include: partial pressure of venous oxygen (PvO_2), partial pressure of venous carbon dioxide ($PvCO_2$), HCO_3, oxygen saturation (SvO_2), and pH.

Table 3-2 Blood Gasses

Blood Gasses	
Arterial	**Capillary/ Venous**
PaO_2	PvO_2
$PaCO_2$	$PvCO_2$
HCO_3	HCO_3
SaO_2	SvO_2
pH	pH

A blood lactate level will be collected with each blood gas.

3.3.1.6 Echocardiogram (ECHO)

Echocardiograms (ECHO) are used to rule out congenital heart defects and to assess the pulmonary artery (PA) and/or right ventricular (RV) pressures. Specifically, the following parameters will be recorded: tricuspid regurgitation (TR) jet velocity (if available); pulmonary regurgitation (PR) jet velocity (if available); direction of shunting through patent ductus arteriosus (PDA), atrial septal defect (ASD), ventricle septal defect (VSD) or patent foramen ovale (PFO) (if present); evidence and degree of RV dilation; and interventricular septal position.

An ECHO will be performed at Screening and repeated at Day 7 and Day 14, or prior to hospital discharge if that occurs prior to Day 14. Additionally, an ECHO will be performed prior to weaning study drug and within 48 hours of study drug discontinuation.

3.3.1.7 N-Terminal pro B-Type Natriuretic Peptide (NT-proBNP)

NT-proBNP is a cardiac biomarker associated with volume or pressure overload of the right ventricle. Subjects will have samples for NT-proBNP collected at Baseline, daily during the first 72 hours of study drug treatment, Day 7, and at Day 14, or prior to hospital discharge if that occurs prior to Day 14. Additionally, subjects will have samples collected for NT-proBNP prior to weaning study drug and at the time of study drug discontinuation.

3.3.2 Safety

3.3.2.1 Physical Examination

A physical examination will be conducted at Screening, Baseline, daily during the first 72 hours of study drug treatment, on Day 7, and Day 14. Additionally, subjects will have a physical examination prior to weaning study drug, within 24 hours of study drug discontinuation, and prior to hospital discharge, or at 4 weeks after discontinuing study drug, whichever comes first. Length and weight will be collected at Baseline and at the final follow-up visit. The Baseline weight will be used to calculate all doses of study drug.

3.3.2.2 Vital Signs

Vital signs will include blood pressure (BP), heart rate (HR), respiratory rate (RR), temperature (temp), and oxygen saturation (SpO_2). Both pre- and post-ductal SpO_2 will be collected for the first 72 hours. Vital signs will be collected at Screening, Baseline, and during study drug administration as follows: approximately every 6 hours for the first 72 hours, daily starting on the fourth day for as long as the subject is on study drug, prior to weaning, every 24 hours while weaning, at the time of study drug discontinuation, and 48 hours after study drug discontinuation. Vital signs will also be collected prior to hospital discharge or at the 4 week follow-up after discontinuing study drug, whichever comes first. Additionally, BP, HR, and SpO_2 will be collected with each study drug dose change.

3.3.2.3 Clinical Laboratory Assessments

3.3.2.3.1 Chemistries, Hematology and Liver Function Tests

A complete metabolic, hematologic, and liver function panel will be assessed at Baseline, Day 7, and Day 14. Additionally, subjects will have clinical laboratory assessments prior to weaning study drug, within 12 hours of study drug discontinuation, 48 hours after discontinuing study drug, and prior to hospital discharge or at the 4 week follow-up after discontinuing study drug, whichever comes first. Table 3-3 summarizes each laboratory parameter to be assessed.

Table 3-3 Chemistries, Hematology and Liver Function Tests

Chemistries	Hematology	Liver Function Tests (LFTs)
Sodium Potassium Chloride Bicarbonate/ CO_2 Blood Urea Nitrogen (BUN) Creatinine Glucose Calcium Albumin Lactate[a]	Red Blood Cell Count Hematocrit Hemoglobin Platelet Count White Blood Cell Count *(no differential)* Prothrombin time	Alkaline Phosphatase Alanine Aminotransferase (ALT) Aspartate Aminotransferase (AST) Total Bilirubin

[a]See Section 3.3.1.5

3.3.2.4 Adverse Events (AEs)

Documentation of AEs will be recorded in the eCRF from the time informed consent is provided until time of screen failure, time subject is withdrawn from study, time of hospital discharge, death, or until 4 weeks after the last dose of study drug, whichever comes first. All AEs should be followed until either resolution (or return to normal or Baseline values), until judged by the Investigator to no longer be clinically significant or until 4 weeks after last dose of study drug. Subjects with ongoing AEs at the time of hospital discharge will continue to be followed for their AEs until either resolution (or return to normal or Baseline values), until judged by the Investigator to no longer be clinically significant, or until 4 weeks after last dose of study drug. All SAEs will be followed until resolution, death, or the subject is lost to follow-up, even if they are ongoing more than 4 weeks after the last dose of study drug. Sections 9 and 15.1 provide the definitions and guidelines for recording AEs. If the subject receives Remodulin after hospital discharge, beyond Day 56/End of study, or following withdrawal from the study, AEs/SAEs will be subject to AE/SAE reporting under local government post-marketing AE/SAE reporting requirements.

3.3.3 Pharmacokinetics

Blood samples will be collected from subjects on study drug for treprostinil pharmacokinetic (PK) analysis. A venous or capillary blood sample, rather than arterial blood sample should be collected. Up to two samples will be taken from each subject:

- After 24 hours (+6 hours) of initiating study drug dosing (collected at least 2 hours after the last dose change)
- Immediately prior to beginning to down titrate (wean) study drug, or on Study Day 28 if the subject will continue on Remodulin

- A second sample is not required in subjects who are unblinded (after Day 14 or due to clinical worsening event) and identified to be on placebo

If any early or late blood draws are performed, the time and reason should be recorded in the eCRF. Appendix 15.2 contains a detailed description for the pharmacokinetic blood collection, processing, storage, and shipment of all samples.

3.4 NUMBER OF CENTERS

Approximately 40 centers are planned.

3.5 NUMBER OF SUBJECTS

Approximately 70 subjects will be randomized (1:1) to either receive treatment with Remodulin or placebo to provide 66 evaluable neonates. Enrollment will be closed once 66 evaluable subjects have been enrolled. No more than 32 subjects with a diagnosis of PPHN associated with CDH will be enrolled; these subjects will be evenly enrolled (1:1) into the Remodulin and placebo groups.

3.6 ESTIMATED STUDY DURATION

No subject will receive study drug for greater than 28 days (4 weeks). Post-treatment data will be collected until death, time of hospital discharge, time of study withdrawal, or until 4 weeks after last dose of study drug, whichever comes first. Subjects with ongoing AEs at the time of hospital discharge or study withdrawal will be followed for their AEs until either resolution (or return to normal or Baseline values), until judged by the Investigator to no longer be clinically significant, or for up to 4 weeks beyond the subject's last dose of study drug. Therefore, the maximum amount of time a subject randomized to study drug would be in the study is 56 days (a maximum of 28 days of study drug, plus 4 week follow-up (28 days) after last dose/discontinuing study drug). Per the Investigator's discretion, if Remodulin treatment is needed beyond Day 28, subjects will be transitioned to commercial product; Day 28 will be considered as the last day of study drug administration. These subjects will continued to be followed in the study until they have reached Day 56 (4 weeks after last dose of study drug), have been discharged from the hospital or withdrawn from the study, whichever comes first.

The study will be completed once 66 evaluable subjects have been enrolled and completed the last patient last visit/assessment.

4 SUBJECT ELIGIBILITY

4.1 INCLUSION CRITERIA

A subject is eligible to participate if the following criteria are met:

1. Parent(s) or legal guardian provides consent for the subject to participate, as per institutional policy.
2. Weight at least 2 kg at Screening.
3. Gestational age of at least 34 weeks and is ≤14 days old at Screening.
4. Diagnosis of PPHN, which is either idiopathic in nature or associated with the following: MAS, pneumonia, RDS, sepsis, birth hypoxia, perinatal encephalopathy or unilateral CDH.
5. Currently requiring ventilator support.
6. Two consecutive OIs of 15 or greater separated by at least 30 minutes, after receiving iNO for at least 3 hours.
7. Echocardiographic evidence of PH (e.g., ductal shunting, significant TR) with elevated RV pressures).
8. Have venous access (central line or peripherally inserted central venous catheter [PICC, PCVC]) for the administration of study drug. In the event central venous access cannot be established or in the opinion of the Investigator the patient is too unstable to attempt to establish a central venous access line for IV administration of study drug, subjects who are candidates for administration of study drug as a continuous SC infusion may be enrolled.

4.2 EXCLUSION CRITERIA

A subject is ineligible for participation if any of the following criteria are met:

1. Previous or concurrent use of a PDE-5i, ERA or prostanoid. Previous receipt of prostaglandin E1 for ductal patency is allowed.
2. Significant congenital heart disease (CHD) as detected by ECHO (excluding presence of minor defects such as small secundum ASD, minor valvular abnormalities, or expected transitional findings such as a PFO, or PDA. Subjects with small muscular, restrictive VSD may be enrolled).
3. Clinically significant, untreated active pneumothorax at Screening.
4. Evidence of clinically significant bleeding (e.g., hemodynamic instability or requiring transfusion) at Screening. Note: history of a transfusion is not necessarily an exclusion criterion.
5. Necrotizing entercolitis; defined as Bells stage II or greater at Screening.
6. Uncontrolled hypotension; defined as mean systemic pressures less than or equal to 35mmHg at Screening.

7. Uncontrolled coagulopathy and/or untreated thrombocytopenia; defined as <50,000 platelets /μL at Screening.
8. History of severe (Grade 3 or 4) intracranial hemorrhage at Screening. Note: a cranial ultrasonography is not required during Screening.
9. Currently receiving ECMO or has immediate plans to initiate ECMO.
10. Expected duration on mechanical ventilation of less than 48 hours.
11. Life expectancy is less than two months or has a lethal chromosomal anomaly.
12. Contraindication to ECMO.
13. Bilateral congenital diaphragmatic hernia.
14. Active seizures at Screening.
15. Currently participating in another clinical drug study (excluding observational registries).

4.3 PRESCRIBED THERAPY

4.3.1 Concomitant Medications

All subjects will be concurrently receiving iNO prior to randomization. Subjects should be adequately treated (as determined by the Investigator) with standard of care treatments for PPHN (e.g., inotropes, opioids, sedation) prior to enrollment and during the study. Doses of medications should be adjusted as needed during the study. All concomitant medications will be recorded in the subject's eCRF up until 48 hours after discontinuation of study drug. Any concomitant medications used in the treatment of an AE or SAE will be recorded even if it occurs more than 48 hours after discontinuation of study drug.

Caution should be used with cytochrome P450 (CYP) 2C8 enzyme inducers/inhibitors, such as rifampin or gemfibrozil, as plasma concentrations of treprostinil may be altered. Concomitant administration of Remodulin with diuretics, antihypertensive agents or other vasodilators may increase the risk of symptomatic hypotension. Remodulin inhibits platelet aggregation, there may be an increased risk of bleeding when administered with other anticoagulants, such as warfarin, heparin, or NSAIDs.

4.3.1.1 Inotropic Dose Changes

Doses of inotropic and vasoactive agents (e.g., dopamine, epinephrine, dobutamine, milrinone, vasopressin, norepinephrine) will be recorded with each dose change of study drug.

4.3.1.2 Initiation of a Pulmonary Vasodilator Therapy

If the Investigator initiates a targeted pulmonary vasodilator (after meeting the requirements outlined in Section 3.3.1.1.1) during the first 14 days after randomization, the subject will meet the definition of the primary endpoint of clinical worsening.

Subjects randomized to study drug who meet the definition of clinical worsening may continue to receive study drug for a total of up to 28 days at the discretion of the Investigator.

5 SUBJECT ENROLLMENT

5.1 TREATMENT ASSIGNMENT

Subjects will be randomized (1:1) to receive treatment with Remodulin or placebo.

5.2 RANDOMIZATION

An Interactive Web Response System (IWRS) will be utilized for the central randomization procedure. Subjects will be randomized in a ratio between active and placebo of 1:1. No more than 32 evaluable subjects with a diagnosis of PPHN associated with CDH will be enrolled; these subjects will be balanced between the treatment groups.

5.3 BLINDING

This will be a double-blind, placebo controlled study. Subjects will be randomly allocated to Remodulin or placebo via an IWRS system. Investigators, research staff, attending clinicians, NICU staff, and parents will remain blind to the treatment allocation, unless certain criteria for unblinding are met. Some differences in packaging of investigational product may be observed during the study, but pharmacy personnel will not be made aware of the actual treatment assignment. The pharmacist must not communicate with the Investigator or any members of the clinical team about the appearance of vials used in dose preparation. No additional packaging or wrapping is required prior to dispensing the prepared syringe to the floor. Once prepared, the appearance of active and placebo doses are identical.

Access to treatment assignment is outlined in Section 6.2.

6 DRUGS AND DOSING

6.1 DRUG DOSAGE, ADMINISTRATION AND SCHEDULE

6.1.1 General Information

Study drug (Remodulin or placebo) will be supplied in multiple-dose 20mL glass vials containing 1mg/mL treprostinil or placebo. Vials are multi-use and may be used up to 30 days after initial puncture to prepare multiple doses/syringes for the assigned subject. A new vial should be used for each subject.

6.1.2 Dose and Administration of Study Drug

This study aims to evaluate Remodulin administered as a continuous IV infusion in a neonate population. A venous access (preferred via central line (e.g., umbilical venous catheter [UVC] or peripherally inserted central venous catheter [PICC, PCVC]) is required for the IV administration of study drug. Currently, there are no data to confirm whether Remodulin is compatible and may be administered in the same line/lumen with other IV administered agents; however, compatibility studies are planned. Therefore, one line or lumen must be dedicated solely to study drug when administering as a continuous IV infusion until the Investigator is notified by United Therapeutics of the outcome of the compatibility studies. Once compatibility with other IV agents has been confirmed, study drug may be administered in accordance with the data provided. If clinically necessary, a temporary peripheral IV cannula, preferably placed in a large vein, may be used (Remodulin Package Insert or Summary of Product Characteristics). However, use of a peripheral IV infusion may be associated with an increased risk of thrombophlebitis and administration should be short term (Remodulin Package Insert or Summary of Product Characteristics).

In the event dedicated central venous access cannot be established, or in the opinion of the Investigator the patient is too unstable to attempt to establish a dedicated central venous access line for IV administration of study drug, study drug may be initiated as a continuous SC infusion at the discretion of the Investigator. Subjects initiated on IV administration of study drug who lose venous access may be transitioned to SC administration. Remodulin is bioequivalent between the SC and IV route. Therefore, no dose adjustment in study drug is needed if the SC route is utilized (16, 17).

Study drug must be diluted with high-pH glycine diluent (Sterile Diluent for Remodulin, Sterile Diluent for Flolan, or Sterile Diluent for Epoprostenol Sodium), Sterile Water for Injection, or 0.9% Sodium Chloride Injection, prior to IV administration as a continuous infusion using an infusion pump designed for intravenous drug delivery.

Diluted Remodulin has been shown to be stable at ambient temperature for up to 52 hours at concentrations as low as 0.00025mg/mL (250ng/mL) (e.g., infusion cassettes/syringes should be changed at least every 48 hours).

If study drug will be administered as a continuous SC infusion, dilution of study drug is usually not required; however, based upon the selected SC infusion pump flow rate capabilities, the subject's dose weight, and dose in this neonate patient population, dilution may be needed for SC administration (especially for smaller babies and lower doses, or during weaning of study drug). If dilution is required for SC administration, Sterile Water for Injection or 0.9% Sodium Chloride for Injection should be used.

Do not flush study drug line and use caution when changing the study drug infusion line to avoid an accidental bolus/overdosage.

6.1.2.1 Calculating the Study Drug Dilution

Prior to calculating the subject dose of study drug, the following information is needed: volume of infusion syringe or cassette, dose (ng/kg/min; nanogram/kilogram/minute) and weight (kg). The starting dose is 1ng/kg/min. The subject's weight from Baseline should be used to calculate the dose throughout the study period.

Study drug will be diluted to the appropriate concentration depending on the individual's dose and infusion rate for intravenous, or subcutaneous (if applicable) infusion. A separate study drug preparation form may be used to document preparation of dilutions.

Step 1: Calculate the concentration of the dilution to prepare based on subject's Baseline weight, dose and infusion rate

$$Diluted\ study\ drug\ conc.\left(\frac{mg}{mL}\right) = \frac{dose\ (ng/kg/min) x\ Weight\ (kg) x\ 0.00006*}{infusion\ rate\left(\frac{mL}{hr}\right)}$$

** Conversion factor of 0.00006 = 60 min/hour x 0.000001 mg/ng*

Next, the amount of study drug from the 1mg/mL study drug vial needed to make the required diluted concentration for the given syringe size can be calculated using the following formula:

Step 2: Calculate the amount of study drug need to prepare the desired concentration

$$Amount\ of\ study\ drug\ (mL) = \frac{Diluted\ study\ drug\ conc.(mg/mL) x\ Syringe\ Volume\ (mL)}{1\ mg/mL\ Vial\ Strength}$$

The calculated amount of study drug from the 1mg/mL vial is then added to the reservoir along with the sufficient volume of diluent to achieve the desired total volume in the syringe pump.

Study drug may be continually titrated (i.e. up-titration and weaning) during the course of the trial. There will be multiple dose titrations occurring and the choice in concentration should be able to account for multiple titrations to limit the amount of times an infusion syringe or cassette must be prepared or changed.

The concentration should be increased when the volume required to deliver the dose exceeds the ideal fluid intake. Increasing the concentration will decrease the flow rate and volume of study drug administered while allowing for continued dose titrations.

6.1.3 Dose Initiation and Titration

The starting dose of study drug is 1ng/kg/min, which is not anticipated to provide clinical effects. The dose of study drug should be increased by up to 2ng/kg/min every 2 hours, as tolerated and clinically indicated by the physician, based upon the OI; when the OI is no longer calculable, the FiO_2 will be used to guide dosing. As some subcutaneous infusion pumps may not accommodate a starting dose of exactly 1ng/kg/min, the site may proceed with a starting dose as close to 1ng/kg/min as possible. The initial starting dose should not exceed 2ng/kg/min and should be increased by approximately 1-2ng/kg/min every 2 hours as tolerated and clinically indicated by the

physician. Subject response to study drug is individualized; not all subjects will tolerate the same rate of titration and clinically beneficial doses will vary. There is no maximum dose limit. Titration will be made per the subject's response in clinical symptoms.

If the OI is 15 or greater, the dose of study drug should be increased in the absence of dose-limiting adverse events (e.g., hypotension). If the OI is between 10 -14 and the study drug dose is ≤10ng/kg/min, the dose should continue to be increased, as tolerated. If the study drug dose is >10ng/kg/min and the OI is between 10 -14, any further dose escalation will be left to the discretion of the clinicians/Investigators according to the clinical condition of the subject, and the perceived need for additional pulmonary vasodilation. Once the OI is <10 and iNO has been discontinued, study drug weaning can begin (Section 6.1.4).

If the OI cannot be calculated, dose adjustments will be based upon FiO_2. The study drug dose should be increased when the FiO_2 is ≥60% in the absence of dose-limiting adverse events (e.g., hypotension). Once the FiO_2 is <60% and iNO has been discontinued, weaning of study drug can begin. Table 6-1 below describes the suggested dose titration parameters.

Table 6-1 Suggested Study Drug Dose Titration Parameters

Oxygenation Index	**FiO_2** ***(To be used when OI is not calculable)***	**Dosing Strategy**
≥15	≥60%	Dose increase, as tolerated
10-14 *(dose >10 ng/kg/min)*	--	Hold dose or dose increase if clinical condition warrants further pulmonary vasodilation.
10-14 *(dose ≤10 ng/kg/min)*	--	Dose increase, as tolerated
<10	<60%	Begin weaning. The iNO should be weaned and discontinued prior to initiating weaning of study drug.

Subjects may continue on study drug for up to 28 days if clinically indicated. Per the investigator's discretion, if the subject is treated with Remodulin beyond Day 28, Day 28 will be considered as the last day of study drug administration. These subjects will continue to be followed in the study until they have reached Day 56 (4 weeks after last dose of study drug) or have been discharged from the hospital, whichever comes first.

6.1.4 Dose Weaning

Abrupt cessation of study drug will be avoided due to the risk of rebound pulmonary hypertension. Inhaled NO should be weaned and discontinued prior to initiating weaning of study drug. When the subject has reached the treatment goal and is ready to start weaning, the dose of study drug will be held constant at the same dose for at least 12 hours prior to initiating down titration. It is recommended the dose of study drug be decreased by no more than 10ng/kg/min per day either in the same incremental manner as the dose was increased or as determined by the Investigator. Dose decreases in increments greater than 5ng/kg/min are recommended to be avoided, but faster weaning may occur if required per subject care.

If withdrawal from study drug is warranted, the dose of study drug will be weaned until discontinued.

6.1.5 Initiation of ECMO

Subjects randomized to study drug may continue to receive study drug during ECMO at the pre-ECMO dose. Subjects should not be unblinded upon initiation of ECMO, unless required for purposes of medically managing the subject. At the conclusion of ECMO, weaning of study drug can begin per the Investigator's discretion.

6.2 ACCESS TO BLINDED TREATMENT ASSIGNMENT

In the event of a medical emergency that requires immediate unblinding, an unblinding call may be made to determine treatment assignment. The identity of a subject's treatment assignment, should it need to be obtained, will occur through an unblinding call to the 24 hour [redacted]. Investigators will be permitted to access the treatment assignment upon the subject meeting the criterion for clinical worsening or after the completion of Day 14 if required for purposes of medically managing the subject (e.g., another prostacyclin will be initiated). Subjects randomized to placebo may be discontinued from study drug at that time. Subjects randomized to Remodulin who have residual or chronic pulmonary hypertension that does not fully resolve by Day 14 may continue to receive study drug for up to an additional 14 days (for a total of up to 28 days) per the Investigator's discretion. Subjects who have PPHN resolved by Day 14, who have already begun weaning by Day 14 or for whom it is anticipated that weaning of study drug will begin within

shortly after completing Day 14, or who are withdrawn from the study should remain blinded. All attempts should be made to maintain the blind during the study.

6.3 COMPLIANCE

The study will occur within the intensive care unit. All dosing will be administered by qualified medical personnel. Accurate pharmacy and clinical records will be maintained to ensure appropriate doses and dose adjustments are made.

7 EXPERIMENTAL PROCEDURES

7.1 SCREENING

Screening will occur once written informed consent has been obtained from the parent(s) or legal guardian(s). Some Screening and Baseline assessments may be combined if conducted within 3 hours of randomization (noted with "*" below).

Screening activities will include the following:

- Informed consent
- Confirmation of inclusion/exclusion criteria
- Maternal and child history
    - Including birth weight, and the one and five-minute Apgar score
- Physical examination*
- Vital signs (BP, HR, Temp, pre and post-ductal SpO_2)*
- OI assessment*
- Record FiO_2 and MAP (including type of ventilation – high frequency vs. traditional)*
- Arterial blood gas*
- Echocardiogram
- Record concomitant medications
- Record any AEs once informed consent has been provided

7.2 BASELINE

Once all Screening activities have taken place, the following Baseline activities will occur. Once Baseline assessments have been completed and eligibility confirmed, subjects may be randomized in the IWRS. Study drug should be initiated as soon as possible after randomization.

- Physical examination (including length and weight)*
- Vital signs (BP, HR, Temp, pre- and post-ductal SpO_2)*
- OI assessment*

- Record FiO_2 and MAP (including type of ventilation – high frequency vs. traditional)*
- Arterial blood gas*
- Clinical laboratory assessments (See Section 3.3.2.3)
- NT-proBNP
- Randomization
- Initiation of study drug
- Assess clinical worsening
- Record concomitant medications
- Record any AEs

Some Screening and Baseline assessments may be combined (i.e., not repeated) if conducted within 3 hours of randomization (noted with "*").

7.3 TREATMENT PHASE

7.3.1 First 72 Hours

The following assessments will be obtained during the first 72 hours of study drug administration.

- Physical examination (once daily)
- Vital signs approximately every 6 hours (BP, RR, HR, Temp, pre- and post-ductal SpO_2)
- OI assessment approximately every 6 hours (as long as the subject is on mechanical ventilation and ABGs are obtained)
- FiO_2; approximately every 6 hours
- MAP approximately every 6 hours (as long as the subject is on mechanical ventilation)
- Blood gases approximately every 6 hours (ABG if possible, otherwise CBGs/VBGs)
- NT-proBNP (once daily)
- Record concomitant medications
- Continue study drug, up-titrating as needed
  - BP, HR, and SpO_2 will also be collected with each study drug dose change
  - Record doses of inotropes with each study drug dose change
- Record AEs
- Collect PK sample 24 hours after the start of study drug dosing. Sample should be collected at least 2 hours after the last dose change (See Section 3.3.3 and Appendix 15.2)
- Assess clinical worsening (throughout the 14 day study period)

7.3.2 Study Day 4 Throughout Duration of Study Drug Therapy

The following assessments will be obtained daily starting on the fourth day of study drug administration and continue throughout the duration of study drug therapy:

- Vital signs (BP, RR, HR, Temp, SpO_2)
- OI assessment (as long as the subject is on mechanical ventilation and ABGs are obtained)

- FiO_2
- MAP (as long as the subject is on mechanical ventilation)
- Blood gases (ABG if possible, otherwise CBGs/VBGs)
- Record concomitant medications
- Continue study drug, up-titrating as needed
  - BP, HR, and SpO_2 will also be collected with each study drug dose change
  - Record doses of inotropes with each study drug dose change
- Record AEs
- Assess clinical worsening (throughout the 14 day period)

Subjects who have residual or chronic pulmonary hypertension that does not fully resolve by Day 14 may continue to receive study drug for up to an additional 14 days (for a total of up to 28 days) per the Investigator's discretion.

7.3.2.1 Study Day 7 and Day 14

The following assessments should be performed on study Day 7 and Day 14 regardless if the subject has already been weaned from study drug. If the subject will be discharged from the hospital prior to Day 14, the Day 14 assessments should be completed prior to hospital discharge.

- Physical examination
- Vital signs (BP, RR, HR, Temp, SpO_2)
- OI assessment (as long as the subject is on mechanical ventilation and ABGs are obtained)
- FiO_2
- MAP (as long as the subject is on mechanical ventilation)
- Blood gases (ABG if possible, otherwise CBGs/VBGs)
- Clinical laboratory assessments (See Section 3.3.2.3)
- NT-proBNP
- Echocardiogram
- Record concomitant medications
- Continue study drug, up-titrating as needed
  - BP, HR, and SpO_2 will also be collected with each study drug dose change
  - Record doses of inotropes with each study drug dose change
- Record AEs
- Assess clinical worsening (throughout the 14-day period)

7.3.3 Study Drug Discontinuation

7.3.3.1 Prior to Weaning or Discontinuing Study Drug

"Prior to wean" assessments will be collected after the dose has been maintained for at least 12 hours and no more than 1 hour prior to beginning to wean study drug. In the event that the subject

will continue on commercial Remodulin beyond Day 28, these assessments should take place on Day 28.

- Physical examination
- Vital signs (BP, RR, HR, Temp, SpO_2)
- OI assessment (as long as the subject is on mechanical ventilation and ABGs are obtained)
- FiO_2
- MAP (as long as the subject is on mechanical ventilation)
- Blood gases (ABG if possible, otherwise CBGs/VBGs)
- Clinical laboratory assessments (See Section 3.3.2.3)
- Echocardiogram
- NT-proBNP
- Collect PK sample (See Section 3.3.3 and Appendix 15.2)
- Record concomitant medications
- Record doses of inotropes
- Record AEs

7.3.3.2 Daily While Weaning Study Drug

The following will be collected every day while weaning study drug.

- Physical examination
- Vital signs (BP, RR, HR, Temp, SpO_2)
  - BP, HR, and SpO_2 will also be collected with each study drug dose change
- FiO_2
- MAP (if the subject is on mechanical ventilation)
- Record concomitant medications
  - Record doses of inotropes with each study drug dose change
- Record AEs

These assessments will not be performed in subjects who continue on commercial Remodulin beyond Day 28.

7.3.3.3 Study Drug Discontinuation

The following will be collected immediately (within 12 hours) after study drug discontinuation.

- Physical examination
- Vital signs (BP, RR, HR, Temp, SpO_2)
- FiO_2
- MAP (if the subject is on mechanical ventilation)

- Clinical laboratory assessments (See Section 3.3.2.3)
- NT-proBNP
- Blood gasses (if arterial access is not available, collect CBGs/VBGs)
- Record concomitant medications (until 48 hours after the subject has stopped receiving study drug)
  - Record doses of inotropes
- Record AEs

These assessments will not be performed in subjects who continue on commercial Remodulin beyond Day 28.

7.3.3.4 48 Hours after Study Drug Discontinuation

The following will be collected 48 hours ± 4 hours after study drug discontinuation.

- Vital signs
- Clinical laboratory assessments (See Section 3.3.2.3)
- Echocardiogram
- Record concomitant medications (until 48 hours after the subject has stopped receiving study drug)
  - Record doses of inotropes
- Record AEs

These assessments will not be performed in subjects who continue on commercial Remodulin beyond Day 28.

7.3.4 Follow-up/End of Study

The following assessments will be conducted during a final assessment visit at the time of withdrawal from the study, hospital discharge, or at 4 weeks after discontinuing study drug, whichever comes first, for all subjects who receive study drug. In the event that a subject randomized to Remodulin will receive commercial Remodulin beyond Day 28, and the subject has not been discharged from the hospital or withdrawn from the study, these assessments should take place on Day 56.

- Physical exam including height and weight
- Vital signs (BP, RR, HR, Temp, SpO_2)
- Clinical laboratory assessments (See Section 3.3.2.3)
- Record AEs

Subjects with ongoing AEs at the time of hospital discharge will continue to be followed for their AEs until either resolution (or return to normal or Baseline values), until judged by the Investigator to no longer be clinically significant, or until 4 weeks after last dose of study drug.

8 STUDY TERMINATION

8.1 CRITERIA FOR SUBJECT WITHDRAWAL

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

- The subject's parent or legal guardian wishes to withdraw the subject from further participation.
- A serious or life-threatening AE occurs or the Investigator considers that it is necessary to discontinue study drug to protect the safety of the subject.
- The subject did not initiate study drug.

If a subject is discontinued from the study prematurely, the Investigator must complete all applicable eCRF records, including the End of Study Record for that subject. If study drug has been administered, the Investigator should make every effort to perform all scheduled evaluations. In the event that a subject discontinues study drug prematurely due to an AE, the subject will be followed until either the Investigator determines that the AE has resolved, it is no longer considered clinically significant, the subject is lost to further follow-up, or for 4 weeks after last dose of study drug. SAEs will be followed by United Therapeutics Corporation Global Drug Safety until resolution, death, or the subject is lost to follow-up.

If withdrawal from study drug is warranted, the dose of study drug will be weaned until discontinued. Abrupt cessation of study drug will be avoided due to the risk of rebound pulmonary hypertension.

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 adverse events 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 A 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.
- US FDA, European, or national 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 (AE)

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

9.1.2 Serious Adverse Event (SAE)

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.

9.1.3 Suspected Adverse Reaction

Suspected adverse reaction means any AE for which there is a reasonable possibility that the study drug caused the AE. For the purposes of investigational new drug (IND) safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the study drug and the AE.

9.1.4 Unexpected Adverse Event

An event is 'unexpected' if its specificity or severity is not consistent with the current clinical Investigator Brochure. It could include an event that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differs from the event because of greater severity or specificity. Reports of death resulting from an AE are considered 'unexpected' unless the possibility of a fatal outcome from that AE is stated in the labeling.

9.1.5 Disease Related Events

PPHN is often associated with signs and symptoms of perinatal distress, including but not limited to, those listed in Table 9-1. These events are anticipated to occur in the study population at some frequency independent of drug exposure. These events should be clearly documented in the subject medical record and identified as signs/symptoms of underlying disease under study.

Events that occur during the course of the study that are listed in Table 9-1 and felt to be related to the underlying disease under study by the Investigator will be recorded in the eCRF as disease related events. Events that are either serious or considered unusual with respect to intensity, frequency, or duration, or there is a reasonable possibility that it may have been caused by study drug as determined by the Investigator will also be recorded as an AE. All deaths, regardless of underlying cause, will be reported as an SAE.

Table 9-1 Expected Events Attributable to PPHN (System Organ Class and PREFERRED Term, Ver. 17.0)

Hypoxia (Respiratory, thoracic & mediastinal disorders; HYPOXIA)	Pallor (Vascular disorders; PALLOR)
Cold extremities (General disorders and administration site conditions; PERIPHERAL COLDNESS)	Cyanosis (Cardiac disorders; CYANOSIS)
Cardiac arrhythmia (Cardiac disorders; ARRHYTHMIA)	Coagulopathy (Blood and lymphatic system disorders, COAGULOPATHY)
Tachypnea (Respiratory, thoracic & mediastinal disorders; TACHYPNOEA)	Respiratory distress (Respiratory, thoracic and mediastinal disorders; RESPIRATORY DISTRESS)
Polycythemia (Blood and lymphatic system disorders, POLYCYTHAEMIA)	Hyperviscosity syndrome (Blood and lymphatic system disorders, HYPERVISCOSITY SYNDROME)
Cardiovascular collapse (Vascular disorders; CIRCULATORY COLLAPSE)	Asphyxia (Respiratory, thoracic and mediastinal disorders; ASPHYXIA)
Postoperative hypotension (Vascular disorders, PROCEDURAL HYPOTENSION)	Tachycardia (Cardiac disorders; TACHYCARDIA)
Cor pulmonale (Cardiac disorders; COR PULMONALE)	Urine output decreased (Investigations, URINE OUTPUT DECREASED)
Weight loss (Investigations; WEIGHT DECREASED)	Shock (Vascular disorders; SHOCK)
Edema (General disorders and administration site conditions; OEDEMA)	Hepatomegaly (Hepatobiliary disorders; HEPATOMEGALY)
Respiratory failure (Respiratory, thoracic and mediastinal disorders; RESPIRATORY FAILURE)	

9.2 DOCUMENTATION OF ADVERSE EVENTS

An AE or SAE occurring during the study must be documented in the subject's source documents and on the appropriate eCRF page. Information relating to the AE such as onset and cessation date and time, intensity, seriousness, relationship to study drug, and outcome is also to be documented in the eCRF (see Appendix 15.1 for definitions). Serious AEs are to be reported on the SAE Notification Form and submitted within 24 hours to United Therapeutics Global Drug Safety (Section 9.4). Where possible, AEs/SAEs should be recorded using standard medical terminology. 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 (e.g., pneumonia characterized by shortness of breath and wheezing).

9.3 PERIOD OF OBSERVATION

For the purposes of this study, the period of observation starts from the time the informed consent is signed and concludes upon meeting screen failure criteria, at the time of death, at the time of hospital discharge, at the time of withdrawal from the study, or at 4 weeks after last dose of study drug, whichever comes first. Day 28 will be considered as the last day of study drug administration for subjects who continue on Remodulin. Subjects with ongoing AEs at the time of hospital discharge will continue to be followed for their AEs until either resolution (or return to normal or Baseline values), until judged by the Investigator to no longer be clinically significant, or until 4 weeks after last dose of study drug. All SAEs should be followed until resolution, death, or the subject is lost to follow-up, even if they are ongoing more than 4 weeks after the last dose of study drug.

If the subject receives commercial Remodulin after hospital discharge, beyond Day 56/End of study, or following withdrawal from the study, AEs/SAEs will be subject to AE/SAE reporting under local government post-marketing AE/SAE reporting requirements.

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 the Investigator detects an SAE in the study subject after the end of the period of observation, and considers the event possibly related to prior study treatment, he or she should contact the Sponsor to determine how the event should be documented and reported.

9.4 REPORTING RESPONSIBILITIES OF THE INVESTIGATOR

All SAEs, regardless of expectedness or causality, must be reported to the Sponsor by fax [redacted] or email [redacted] within 24 hours of awareness. A completed SAE Notification Form along with any relevant hospital records (e.g., discharge summary), death certificates and autopsy reports (if performed) should be faxed to United Therapeutics Global Drug Safety Department. A follow-up SAE Notification Form must be forwarded to the United Therapeutics Global Drug Safety Department within 24 hours of the receipt

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

9.5 SAFETY REPORTS

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

10 STATISTICAL CONSIDERATIONS

10.1 DATA PROCESSING

Data collection will begin during screening (i.e., once the informed consent form has been signed). Subjects will be assigned a separate screening number until they are randomized, after which a separate subject number will be assigned for subjects enrolled into the study.

Subject data will first be documented in the subject's source documents, and then transferred into the eCRF. All data entered into the eCRF should have a corresponding source document. Site personnel will be responsible for recording all subject data into the eCRF. The eCRF pages are to be reviewed by the Principal Investigator for completeness and accuracy. The Principal Investigator must sign each subject's eCRF to signify their approval of the data. The database will be considered final when all outstanding queries have been resolved and all data management quality control procedures are complete.

10.2 SAMPLE SIZE

Based on the systematic review of use of nitric oxide for respiratory failure in infants by Finer and Barrington, 57.9% (194/335) subjects in control group had an outcome of death or requirement for EMCO (18). In this study, assuming 60% subjects in placebo group and 30% subjects in Remodulin group with an outcome of death, requirement for EMCO, or need for additional PAH therapy, we calculated that 66 subjects (33 subjects per treatment group) will have at least 80%

power to show a significant difference in favor of Remodulin at alpha level of 0.05 (one-sided test). Approximately 70 subjects are planned to be randomized (1:1) to either receive treatment with Remodulin or placebo on top of the standard of care.

10.3 ANALYSIS PLAN

10.3.1 Primary Endpoint

Efficacy analyses will be performed in intention to treatment (ITT) population where ITT population includes all randomized subjects who have successfully initiated the study treatment.

The primary endpoint is clinical worsening (need for additional treatment [initiation of another targeted pulmonary vasodilator therapy], initiation of ECMO or death) between Baseline and Day 14 or time of discharge from the hospital, whichever comes first. It will be analyzed as a binary endpoint using the percentage of subjects who meet the definition of clinical worsening within each treatment group. Subjects who meet the definition of clinical worsening after Day 14 will not be counted towards the primary endpoint. Chi-square test will be used to test for the treatment difference.

10.3.2 Secondary Endpoints

Secondary endpoints (change in OI, P/F ratio, and pre- and post-ductal SpO_2, time on mechanical ventilation, and change in NT-proBNP) will be summarized and tested using group t-test. Kaplan-Meier estimate will be provided for time to event variables (time to discontinuation of iNO, time to initiation of ECMO, and time to clinical worsening) and log-rank test will be used to test the treatment differences.

Plasma samples will be analyzed for treprostinil using a validated bioanalytical plasma assay. Individual and mean treprostinil plasma concentration data, and treprostinil pharmacokinetic parameters, determined as able, will be summarized using descriptive statistics.

10.3.3 Safety Analyses

Safety of study drug in neonates will be evaluated by combined assessments of AEs, clinical laboratory parameters, vitals, and physical examination findings. All subjects who receive 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, incidence of treatment-emergent AEs, and treatment-emergent changes in clinical laboratory parameters will be evaluated.

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

Vital sign and clinical laboratory data collected prior to initiation of study drug 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 safety review will be conducted by a Data Safety Monitoring Board (DSMB) after the first 10 subjects have been randomized to receive study drug and have completed the 14-day study period. A second review will occur once 40 subjects have been enrolled and completed the 14-day study period. Ad hoc meetings may be scheduled at additional enrollment milestones or in response to events related to the safety of study treatment.

10.5 OTHER ANALYSES

Exploratory analyses may be conducted based on available study data, such as at additional time points and calculation of a Total Inotropic Dose Index with each dose change.

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, and SD will be provided.

Plasma concentration data and any applicable derived pharmacokinetic parameters will be summarized and displayed in both tabular and graphical form. Comparative plots of individual concentration data may be produced and summarized across subjects.

10.7 DATA SAFETY MONITORING BOARD (DSMB)

A DSMB will be established for the study, composed of up to four independent members including physicians knowledgeable in the treatment of PPHN and a statistician. The DSMB will meet to monitor the safety of the study as established in a DSMB charter.

11 PACKAGING AND FORMULATION

11.1 CONTENTS OF STUDY DRUG

United Therapeutics will supply study drug (Remodulin or matching placebo) for administration in the study. Study drug will be supplied in 20mL clear glass vials sealed with a rubber-coated stopper and fitted with a cap containing 20mg (1mg/mL) of treprostinil or placebo as sterile solutions in water for injection.

Remodulin Composition Description: 1mg/mL treprostinil. Each mL also contains 5.3mg sodium chloride, 3mg metacresol, 6.3mg sodium citrate, and water for injection. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2.

Placebo Component Description: Sodium Citrate USP/EP/JP, Sodium Chloride USP/EP/JP, Sodium Hydroxide Pellets, Metacresol, Citric Acid (anhydrous). Used to adjust pH, if needed: 1M Citric Acid, 1N NaOH.

11.2 LABELING

Each vial will be labeled in accordance with applicable national regulations, to include at least the following information: investigational product name, trial reference code, concentration, quantity, route of administration, manufacture or expiry date, lot number, Sponsor name, address and

telephone number, and storage conditions. The labels may include blank fields for sites to document the following information, including but not limited to, Investigator name, subject number/initials, and date the vial was opened.

11.3 STORAGE AND HANDLING OF STUDY DRUG

Study drug will be stored at a controlled temperature of 25°C (77°F) with excursions permitted to 15-30°C (59-86°F). Study drug vials should not be frozen or exposed to heat. Temperature excursions should be reported to United Therapeutics as soon as they are identified via email [redacted] and any affected drug should be quarantined until notified by the Sponsor. Study drug should not be used after the expiry date that is stated on the vial. The expiry date refers to the last day of that month. Study drug should not be used if any damage to the vial, discoloration, or other signs of deterioration is noticed. A study drug vial must be used or discarded within 30 days after initial puncture.

Study drug must be diluted to the appropriate concentration based upon the subject weight, dose and fluid constraints (i.e. flow rate) in this neonate patient population. Diluted study drug solution can be administered for up to 52 hours at 37°C when diluted to concentrations as low as 250ng/mL in 0.9% sodium chloride; although it is recommended to change the drug solution every 48 hours.

Selection of Diluent

Route	Diluent	Storage and Administration Limits
IV	Sterile Diluent for Remodulin[1] Sterile Diluent for Flolan Sterile Diluent for Epoprostenol Sodium	Do not use beyond 16 days from date of preparation[2]. Store at room temperature. Syringes may be administered up to 48 hours.
	Sterile water for injection 0.9% Sodium Chloride for Injection	Do not use beyond 52 hours from time of preparation if maintained at room temperature. Syringes may be administered up to 48 hours[3]. Maybe stored up to 24 hours in the refrigerator after preparation. May be administered up to 48 hours once removed from the refrigerator[3].
SC	None	Do not use beyond 76 hours from time of preparation if maintained at room temperature. Syringes may be administered up to 72 hours. May be stored up to 24 hours in the refrigerator after preparation. May be administered up to 72 hours at 37°C once removed from the refrigerator.
	Sterile water for injection 0.9% Sodium Chloride for Injection	Do not use beyond 52 hours from time of preparation if maintained at room temperature. Syringes may be administered up to 48 hours[3]. May be stored up to 24 hours in the refrigerator after preparation. May be administered up to 48 hours once removed from the refrigerator[3].

[1]Sterile Diluent for Remodulin may be provided during the trial once available.
[2]Allows for multiple syringes to be prepared in advance for a subject.
[3]Studies have been performed with concentrations as low as 250ng/mL in 0.9% sodium chloride administered for up to 52 hours at 37°C; although it is recommended to change the drug solution at least every 48 hours.

Currently, there are no data to confirm whether Remodulin is compatible and may be administered in the same line/lumen with other IV administered agents; however, compatibility studies are planned. Therefore, until the Investigator is notified by United Therapeutics of the outcome of the compatibility studies, one line or lumen must be dedicated solely to study drug when administering as a continuous IV infusion.

All study drug must be accounted for and the Investigator will maintain a log sheet of all vials as they are received and used during the study. The pharmacist or appropriate personnel will retain all study drug used for each study subject.

11.4 SUPPLY AND RETURN OF CTM

Study sites will be supplied with a sufficient quantity of study drug to begin enrollment in the study. Appropriate arrangements will be made for resupply to the site with respect to subject enrollment.

All used and unused study drug should be retained by the pharmacist or appropriate personnel at the site (including empty, partially used and unopened vials).

11.5 DRUG ACCOUNTABILITY

The Investigator is responsible for study drug accountability and reconciliation overall and on a per subject basis. Drug accountability records are to be maintained during the study and these records include: the amount of study drug received from the Sponsor, the amount dispensed to each subject, and the amount of unused drug. The quantity of investigational product lost, missing, destroyed, etc. must also be accounted for and documented. At the end of the study, reconciling the delivery records with those of usage and discarded stocks must be possible. Accounts must be given of any discrepancies. Once a representative from the Sponsor is able to confirm drug accountability, study drug will be returned to a Sponsor-designated location for destruction.

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 IRBs/ECs that require it. Any additional national reporting requirements as specified by the applicable regulations, regulatory authorities, or IRB/EC will also be fulfilled during the conduct of the study.

12.2 INFORMED CONSENT REQUIREMENTS

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

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/EC and provide the Sponsor with a copy of the approval letter. The IRB/EC 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/EC 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/EC approval of these amended documents prior to implementation. Copies of the IRB/EC correspondence and approval letters must be provided to the Sponsor.

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

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

12.4 PRESTUDY DOCUMENTATION REQUIREMENTS

Before the commencement of the clinical trial, the following documents will be provided to the site: Investigator's Brochure, protocol, model informed consent form, budget, and clinical trial agreement.

The site will be required to provide the following documents to United Therapeutics Corporation or designee prior to study start: Investigator signature page of the protocol, Form FDA 1572, IRB/EC Composition and Roster, IRB/EC protocol and informed consent approval letters, Curriculum Vitae, financial disclosure forms of study staff listed on the Form FDA 1572, and an authorized 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/EC 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/EC 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

It is understood that the term "Investigator" as used in this protocol and on case report forms refers to the Principal Investigator or a member of the staff that the Principal Investigator designates to perform a certain duty (as documented on the Delegation of Authority Log). The Principal Investigator is ultimately responsible for the conduct of all aspects of the study in accordance with the protocol, even those tasks delegated to others, and ensuring written informed consent is obtained from the parent(s) or legal guardian for each individual participating in this study.

13.1 PROTOCOL AMENDMENTS AND STUDY TERMINATION

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

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

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

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

13.2 STUDY DOCUMENTATION AND STORAGE

In accordance with federal/national regulations, ICH, and GCP guidelines, the Investigator must retain study records for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Where required by other applicable regulatory requirements, the Investigator shall retain the documents for a longer period.

The Investigator must notify United Therapeutics Corporation in writing 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.

14 REFERENCES

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15 APPENDICES

15.1 GUIDELINES AND DEFINITIONS FOR RECORDING ADVERSE EVENTS

For each adverse event, the Investigator will: (1) rate the intensity and seriousness of the AE, (2) estimate the causality of the AE to study drug, and (3) note actions taken to counteract the AE.

Definitions of Intensity, Seriousness, Causality, and Action Taken

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.

- Mild: No limitation of usual activities.
- Moderate: Some limitation of usual activities.
- Severe: Inability to carry out usual activities.

Difference Between "Severe" and "Serious"

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe myocardial infarction); the event itself; however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Causality

An estimate of causality between a specified AE and the study drug is made by the Investigator. Definitions of the categories follow:

- POSSIBLE - the AE MAY have been caused by study drug. There is a reasonable causal relationship between the study drug and the SAE. The event responds to dechallenge. Rechallenge is not required.
- PROBABLE - it is LIKELY that the AE was caused by study drug. There is a reasonable causal relationship between the study drug and the SAE. Dechallenge information is lacking or unclear.
- NOT RELATED - it is UNLIKELY that the AE was caused by study drug. 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.

Action Taken with Test Agent*

The action taken with test agent as a direct result of the AE:

- DOSE NOT CHANGED - there was no alteration in either the dose or regimen of the test agent
- DOSE INCREASED – dose was increased
- DOSE DECREASED – dose was decreased
- DRUG INTERRUPTED - the dose or regimen of the test agent was altered or administration of the test agent was stopped temporarily
- DRUG WITHDRAWN- administration of the test agent was stopped permanently and not restarted. This does not apply if the subject was on drug at the time of death. For this scenario "Dose not changed" would be marked.
- Not Applicable- (i.e., AE occurred prior to administration of test agent)

* Only the last action should be recorded on the CRF.

Outcome

- Fatal – The study subject died
- Not Recovered/Not Resolved – The AE was ongoing at the end of the study/AE observation period
- Recovered/Resolved – The AE resolved
- Recovered/Resolved with Sequelae – The AE is considered resolved; however, there is a residual sequelae
- Recovering/Resolving – The AE is improving but is not yet completely recovered/resolved at the end of study/AE observation period
- Unknown – The outcome of the AE cannot be determined

AE/SAE Start Date verses Serious Date

The AE start date is classified as the first day the subject experiences sign and symptoms of an event and should be entered on the eCRF and SAE Notification Form section "Onset date of symptoms." The date the event became serious is the first day the event meet one of the serious criterion (see section 9.1.2). The start date and date event became serious could be the same date (e.g., clavicle fracture from a fall).

Note: The start date (onset) should never be a date prior to the subject signing the informed consent.

AE/SAE Stop Date

For AEs and SAEs the dates listed on the eCRF and SAE Notification Form will always be the same. For non-fatal events, this is the date the last sign and/or symptom resolved. For fatal events this is the date of Death. If the event Recovered/Resolved with Sequelae enter the date the subject's medical condition resolved or stabilized.

For SAEs follow-up must continue until resolution, death, end of study, or subject is lost to follow-up.

15.2 PHARMACOKINETIC SAMPLE PROCESSING

Collection, Processing and Shipment of Plasma Specimens

Up to 2 blood specimens (approximately 0.5-1mL of blood per sample) for pharmacokinetic analysis will be collected during the study from each subject who receives study drug the following times relative to study drug administration:

- 24 hours (+6 hours) following initiation of study drug dosing (collected at least 2 hours after the last dose change)
- Immediately prior (within 1 hour) to beginning to down titrate (wean) study drug, or on Study Day 28 if the subject continued on IV Remodulin
    - A second sample will not be required in subjects who are unblinded and identified to be on placebo

Time and date of blood draws will be recorded. If any early or late blood draws are performed, the time and reason should be recorded in the eCRF.

Specimen Processing

- Collect approximately 0.5- 1mL blood specimen in a collection tube containing K3-EDTA or K2-EDTA as an anticoagulant and immediately place the specimen on ice.
- Within 1 hour of collection, centrifuge the specimen at 4ºC for 10-15 minutes at 3000g.
- Label the shipping tube with the subject number, and specimen collection time and date.
- Pipette approximately 250µL plasma into a cryogenic storage tube. Pipette the remainder of the plasma into a second, identically labeled cryogenic storage tube for use as a backup specimen for storage at the clinical site.
- Freeze samples immediately at -70-80ºC (-20 to -25ºC permitted) until instructed to ship by Sponsor.

Shipping Procedures

- The sample will be transported on dry ice to the Sponsor-designated laboratory. The backup sample will be retained at the site and transported later in the event of an emergency or if deemed necessary by the Sponsor.
- 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 electronic copy of the packing list (manifest) should be provided to the laboratory in advance of the shipment.
- The bioanalytical lab shipping address and contact person will be provided prior to shipping of samples.

15.3 ADMINISTRATION OF REMODULIN

The preferred method of administration of Remodulin is by central venous access via an umbilical venous catheter (UVC) or peripherally inserted central catheter (PICC). Currently, there are no data to confirm whether Remodulin is compatible and may be administered in the same line/lumen with other IV administered agents; however, compatibility studies are planned. Therefore, one line or lumen must be dedicated solely to study drug when administering as a continuous IV infusion until the Investigator is notified by United Therapeutics of the outcome of the compatibility studies. Once compatibility with other IV agents has been confirmed, study drug may be administered in accordance with the data provided. It is recommended that an infusion set with a 0.22 or 0.2 micron pore size in-line filter should be used for IV administration, unless institutional policies and practices restrict use of in-line filters in this patient population.

If clinically necessary, a temporary peripheral IV cannula, preferably placed in a large vein, may be used for short term administration of study drug (Remodulin Package Insert). However, use of a peripheral IV infusion for more than a few hours may be associated with an increased risk of thrombophlebitis (Remodulin Package Insert).

Due to the inherent risks associated with central venous catheter placement, IV Remodulin was infused peripherally to healthy volunteers in two Phase I, open-label studies (16, 17). In the first study, Remodulin was diluted with 5% dextrose and administered to 15 subjects at a rate of 15ng/kg/minute for 150 minutes (17). No phlebitis was reported during the 150-minute peripheral IV infusion. The most common adverse events were headache (53%), dizziness (27%), and nausea (20%). In the second study, Remodulin was diluted with normal saline and administered to 53 subjects at 10ng/kg/minute for 3 days (16). This longer infusion was more problematic. Although no adverse events were judged to be serious, the most common adverse events involved the infusion site and included infusion site pain (57%), infusion site erythema (55%), infusion site edema (43%), and infusion site tenderness (13%). Other adverse events were mostly typical of prostacyclin administration, including: headache (53%), jaw pain (26%), and nausea (23%). Further analyses of these data to determine the optimal maximum duration of a peripheral infusion of Remodulin have not been conducted.

With any type of line, caution should be taken to ensure that:

1. No other drug or solution is co-administered through the line dedicated solely to study drug until notified by United Therapeutics of the outcome of the compatibility studies. Once compatibility with other IV agents has been confirmed, study drug may be administered in accordance with the data provided.
2. No blood specimens are drawn from the dedicated study drug line; this may lead to a temporary interruption in the study drug infusion.
3. The dedicated study drug line is **not flushed** as is standard nursing practice for most peripheral lines as flushing may lead to the delivery of a bolus dose.

Precautions should be taken to ensure that the study drug infusion continues uninterrupted. Suggested precautions may include labeling the study drug lumen with warnings such as: "Do Not Stop," "Call MD Before Stopping," "Dedicated to study drug," "Do Not Flush," and/or "Do Not Draw Bloods."

In the event dedicated central venous access cannot be established, or in the opinion of the Investigator the patient is too unstable to attempt to establish a dedicated central venous access line for IV administration of study drug, study drug may be initiated as a continuous SC infusion at the discretion of the Investigator. Subjects initiated on IV administration of study drug who lose venous access may be transitioned to SC administration. Remodulin is bioequivalent between the SC and IV route, therefore no dose adjustment is needed if the SC route is utilized.