CLINICAL PROTOCOL

A MULTI-CENTRE, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, TWO-ARMED, PARALLEL GROUP STUDY TO EVALUATE EFFICACY AND SAFETY OF IV SILDENAFIL IN THE TREATMENT OF NEONATES WITH PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN (PPHN) OR HYPOXIC RESPIRATORY FAILURE AND AT RISK FOR PPHN, WITH A LONG TERM FOLLOW-UP INVESTIGATION OF DEVELOPMENTAL PROGRESS 12 AND 24 MONTHS AFTER COMPLETION OF STUDY TREATMENT

Compound:	UK-092,480
Compound Name (if applicable):	Sildenafil
US IND Number (if applicable):	CCI [redacted]
European Clinical Trial Database (EudraCT) Number (if applicable):	2012-002619-24
Protocol Number:	A1481316
Phase:	3

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Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 3	16 Apr 2015	Global changes include: • Made changes to inclusion criteria for clarification and to amend age of subject at enrollment • Clarified the definition of CPR in the exclusion criteria • Modified Study Treatments section to include instructions for double-blind investigational product • Added guidance/advice pertaining to study drug infusion • Clarified requirements for person conducting neurological examination. • Added a note regarding long term visit procedures • Corrected typographical errors • Made multiple changes to text and terms for consistency with current template
Amendment 2	06 May 2014	Global changes include: • Updated audiological tests required. • Clarified certain details based on investigator questions and comments. • Added section Sponsor Qualified Medical Personnel per new protocol template language. • Modified section Adverse Event Reporting and Communication of Results by Pfizer per revised protocol template language.

[redacted]

Document	Version Date	Summary of Changes and Rationale
Amendment 1 Country-specific - France	12 August 2013	Remove PK sample collection from study subjects in France.
Original protocol	23 August 2012	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

[redacted]

Abbreviations:

ABG	Arterial blood gases
ABR	Auditory brainstem response
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
BP	Blood pressure
cGMP	Guanosine monophosphate
CPR	Cardiopulmonary resuscitation
CRA	Clinical research associate
CRF	Case report form
CSR	Clinical study report
DAI	Dosage and Administration Instructions
daPa	Dekapascal
dB	Decibel
DPOAE	Distortion product evoked otoacoustic emissions
EC	Ethics committee
ECMO	Extracorporeal membrane oxygenation
ECV	Ear canal volume
EMA	European Medicines Agency
FiO_2	Fraction of inspired oxygen
HL	Hearing level
HR	Heart rate
HRF	Hypoxic respiratory failure
Hz	Hertz
IB	Investigator's Brochure
iNO	Inhaled nitric oxide
LFT	Liver function test
mmho	Millimho
OAE	Otoacoustic emissions
OI	Oxygenation index
PAH	Pulmonary arterial hypertension
PaO_2	Partial pressure of oxygen dissolved in arterial blood
PDA	Patent ductus arteriosus
PDCO	Paediatric Committee
PDE5	Phosphodiesterase type 5
P/F ratio	Ratio of PaO2 / FiO2
PK	Pharmacokinetics
PPHN	Persistent pulmonary hypertension of the newborn
RR	Respiratory rate
SAE	Serious adverse event
SOP	Standard operating procedures
SpO_2	Oxygen saturation per pulse oximeter
TEOAE	Transient evoked otoacoustic emissions
TPP	Tympanometric peak pressure
ULN	Upper limit of normal
VRA	Visual reinforcement audiometry
Ytm	Static acoustic admittance

PROTOCOL SUMMARY

BACKGROUND AND RATIONALE

Neonates with persistent pulmonary hypertension of the newborn (PPHN) or hypoxic respiratory failure (HRF) who do not respond to comprehensive supportive intensive care measures are typically treated with inhaled nitric oxide (iNO), which is considered standard therapy. Inhaled nitric oxide treatment increases the partial pressure of arterial oxygen (PaO_2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from regions with low ventilation. Inhaled nitric oxide appears to reduce the need for extracorporeal membrane oxygenation (ECMO) in HRF, while mortality is not affected.[1] However, treatment with iNO is not effective for all patients and requires continued intubation and artificial ventilation.

Sildenafil citrate is a selective inhibitor of phosphodiesterase type 5 (PDE5), which is found in high concentrations in the lungs. Inhibition of PDE5 should enhance the vasodilatory effects of naturally occurring and inhaled nitric oxide, promoting relaxation of vascular smooth muscle, and increasing blood flow. Therefore, sildenafil may have utility in the treatment of neonates with PPHN and HRF at risk for PPHN. Case reports of off-label use of sildenafil in conjunction with iNO indicate that sildenafil could enhance the efficacy of iNO and reduce the time on iNO therapy. The effects of the addition of IV sildenafil to standard iNO therapy in the acute stage of this disease will be studied in this clinical study.

OBJECTIVES

- The primary objectives of this study are to evaluate the efficacy and safety of IV sildenafil when added to iNO for the treatment of neonates with PPHN or HRF and at risk for PPHN.

- The secondary objectives of this study are to evaluate the developmental progress of patients with PPHN treated with IV sildenafil or placebo, 12 and 24 months after the end of study treatment.

ENDPOINTS

Part A:

Co-Primary Endpoints: Assessed at Day 14 or hospital discharge, whichever occurs first:

- Time on iNO treatment after initiation of IV study drug for subjects without treatment failure;

- Treatment failure rate, defined as need for additional treatment targeting PPHN, need for ECMO, or death during the study.

Secondary Endpoints: Assessed at Day 14 or hospital discharge, whichever occurs first:

- Time to final weaning of mechanical ventilation for PPHN;
- Time from initiation of study drug to treatment failure; each component will also be evaluated separately;
- Proportion of subjects with individual components of treatment failure (needing additional treatment targeting PPHN, needing ECMO, or who die);
- Change in OI at 6, 12, and 24 hours from baseline;
- Change in differential saturation (pre- and post-ductal) at 6, 12, and 24 hours from baseline;
- Change in P/F ratio at 6, 12, and 24 hours from baseline;
- Sildenafil and its major metabolite UK-103,320 plasma concentrations and the corresponding PK parameters obtained from a population PK analysis; and
- Safety parameters: Incidence and severity of adverse events and abnormal laboratory parameters.

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STUDY DESIGN

Number of Subjects/Sites

Total of 64 subjects (32 for each arm)/A minimum of ~30 sites.

Country Location

Primarily, but not limited to the European Union and North America.

Study Design

This study will be conducted in two parts. Part A is the double-blind phase to assess the efficacy and safety of IV sildenafil versus placebo when added to iNO for no more than 14-days, during the acute phase of the disease, with follow-up at 7 and 28 days after the end of study drug infusion. Part B is the long-term, non-interventional phase, during which all subjects will be encouraged to return at 12 and 24 months after the end of study drug infusion, to take part in developmental assessments, audiological and ophthalmology tests.

Analysis of the double-blind phase of the study (Part A) will be performed when all subjects have completed or discontinued from the double-blind phase, and a study report will be written. Analysis of the non-interventional phase of the study (Part B) will be performed when all subjects have completed or discontinued from the 2-year follow-up visit, and a final study report will be written.

Part A:

This is a multi-center, multi-national, randomized, double-blind (sponsor and investigator), placebo-controlled, parallel group study with a screening phase, treatment phase, and follow-up phase. Neonates who are ≤96 hours of age (at randomization), at least 34 weeks gestational age, receiving iNO at 10-20 ppm while on ≥50% FiO_2 for PPHN or HRF and at risk for PPHN, with oxygenation index (OI) >15 and <60, will be randomized to 1 of 2 parallel arms of study drug treatment: IV sildenafil or IV placebo (1:1 ratio**). Study drug infusion must continue for at least 48 hours,** and may continue for up to 14-days, with or without the administration of additional therapy for PPHN, such as alternative pulmonary vasodilators. **Note: If maintaining study drug infusion for 48 hours is deemed by the investigator to compromise subject safety, the study drug infusion may be stopped, and the subject treated with standard care.**

Weaning from iNO, according to protocol-defined guidelines (See Section 6.2.3), must occur prior to stopping IV study drug, up to the 14-day infusion limit. After study drug is discontinued, the study drug infusion may be restarted within 24 hours as needed based on clinical decline, but not to exceed the 14-day infusion limit. All subjects will be followed up for medical status and adverse events at 7 and 28 days after study drug is discontinued.

Part B:

This is the non-interventional phase of the study, in which developmental progress of subjects from Part A will be assessed. Subjects' parents/legal representative will have the opportunity to return the subjects for two visits, at 12 and 24 month following the end of study drug treatment.

STUDY TREATMENTS

Part A:

All subjects will be treated with standard background therapy, including iNO as specified in the protocol.

Study treatment will be either IV sildenafil, loading dose of 0.1 mg/kg over 30 minutes, followed by maintenance dose of 0.03 mg/kg/h, or IV placebo; infusion to last no more than 14-days. Should a serious or severe event of hypotension develop during the loading dose, per clinical judgment, the investigator has the option to reduce the infusion rate of the loading dose by 50%, or briefly stop the infusion for 15 minutes and then restart the loading dose at half the rate, for the rest of the loading dose.

Part B:

This part of the study is non-interventional.

STATISTICAL METHODS

The primary statistical objective is to test for the superiority of iNO + sildenafil over iNO + placebo for time on iNO treatment after initiation of IV study drug for subjects without treatment failures, and for treatment failure rate.

Sample Size Determination

All subjects who take part in Part A of the study are eligible to take part in Part B, the long-term follow-up part of the study.

Sample size calculation for time on iNO for subjects without treatment failure is based on the internal database at PPD. In the PPD database, there were 101 patients treated with iNO alone who were not treatment failures and met the following entry criteria of this study: age ≤96 hours (at start of study medication), gestational age ≥34 weeks, PPHN patients, 15 < OI <60 at baseline. The mean (S.D.) time on iNO for those 101 patients was 3.4 (1.88) days. It is believed to be clinically relevant if subjects receiving iNO + sildenafil have a 50% reduction in the time on iNO (ie, 1.7 days).

Sample size calculation for the treatment failure rate is based on the iNOmax® pivotal studies (NINOS and CINRGI) (46% and 33% respectively) and the previously completed Pfizer PPHN study A1481157 (2 (7%) out of 29 subjects). Treatment failure rates of 40% and 10% are assumed for the iNO alone arm and the iNO + sildenafil arm respectively.

A total of 64 subjects (32 for each arm) will be enrolled in the study.

Assuming 40% treatment failure rate in the iNO alone arm and 10% failure rate in the iNO + sildenafil arm:

- Time on iNO for subjects without treatment failure: 19 (59%) subjects in iNO alone vs. 29 (91%) subjects in iNO + sildenafil will provide 85% power to detect a mean difference of 1.7 days for time on iNO, assuming mean of 3.4 days for iNO alone and population standard deviation of 1.88 days, at significance level of 0.05 from a 2-sided two sample t-test.

- Treatment failure rate: 32 subjects in each treatment will provide 80% power to detect an absolute difference of 30% (40% vs. 10%) at significance level of 0.05 (2-sided).

Statistical Analysis for Primary Endpoint

Part A:

Time on iNO for subjects without treatment failure will be summarized for each treatment. Treatment comparison will be conducted using analysis of covariance (ANCOVA) adjusting for time on iNO treatment prior to randomization. Mean treatment difference, its 95% confidence interval and p-value will be calculated.

Treatment failure rate and its 95% confidence interval will be calculated for each treatment group. Treatment comparison will be conducted using either Chi-square test or Fisher's exact test, whichever is appropriate. Estimated treatment difference in rates, its 95% confidence interval and p-value will be calculated.

The intent-to-treat (ITT) population will consist of all randomized subjects who receive any infusion of study treatment. The per-protocol (PP) population will be restricted to subjects who complete the study with no major protocol violations. The primary efficacy analysis will be based on the ITT population.

Part B:

For the long-term development assessments, data will be explored through the use of standard presentations of descriptive statistics.

Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Methods

The PK of sildenafil and of UK-103320, the major metabolite in adults, will be characterized using population PK analysis of sildenafil plasma concentration-time data.

Note: PK samples will not be collected from study subjects in France.

SCHEDULE OF ACTIVITIES Part A

Refer to Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.

Protocol Activity	Screening: Up to 96 hr of age	Random-ization: Up to 96 hr of age	Loading Infusion: 0 to 30 min	Maintenance Infusion: >30 min to end of study drug	End of Study Drug Infusion: ≤14-days	Follow up 1: ~7 (±3) days after end of study drug or at discharge	Follow Up 2: 28 (±3) days after end of study drug
Informed Consent[a]	X						
Inclusion/Exclusion Criteria	X						
Physical Examination	X					X	
Medical History, Medication History	X						
Vital Signs[b]	X	X	Every 15 min x 2	Every 15 min x 2, every 30 min x 3 hr, at 12 hr, then every 12 hr	X	X	
Weight	X					X	
Head Circumference	X					X	
Echocardiogram[c]	X						
Cranial Ultrasound[c]	X						
Safety Laboratory Parameters[d]	X[d]			X[d]	X[d]		
Randomization		X					
Administer Study Medication			X	X			
Concurrent/Standard Therapy Monitoring	X	X	X	X	X	If remains hospitalized	If remains hospitalized
Oxygenation Assessments:[e] ABGs, OI, PaO_2, Diff Sat, FiO_2, P/F ratio, Mean Airway Pressure	At least twice with ABG ≥30 min apart			X[e]	X		
Concomitant Medication		X	X	X	X	If remains hospitalized	If remains hospitalized
PK Sampling[f,g,h]		X[f]		X[f]	X[f,g]		
Adverse Events		X	X	X	X	X	X

a. Performed by patient's legal representative.
b. BP, heart rate, respiratory rate, O_2 saturation.
c. An echocardiogram and cranial ultrasound will be performed before randomization if possible or within 24 hours of screening.
d. Performed at screening, once daily for 3 days, then every 48 hours until the end of infusion, plus as clinical need.
e. Performed at screening and targeted at (or as close as possible to) 1, 2, 6, and 12 hours after start of infusion – plus every 12 hours thereafter until the end of infusion whenever clinical samples coincide with these target time points.
f. PK sampling: Prior to start of study drug infusion; at 5 and 30 min after end of loading infusion; between 48 to 72, 96 to 120 hours during infusion; immediately prior to end of infusion.
g. PK sampling: Within 4 to 8, 18 to 24, and 40 to 48 hours after end of study drug infusion.
h. PK samples will not be collected from study subjects in France.

SCHEDULE OF ACTIVITIES Part B

Refer to Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.

Protocol Activity	Screening for Part A	Long-Term Follow-Up Visit 1: 12 months (±2 months) after end of study treatment Part A	Long-Term Follow-Up Visit 2: 24 months (±2 months) after end of study treatment Part A
Informed Consent [a]	X		
Medical History		X	X
Physical Examination [b]		X	X
Audiological evaluation [c]		X	X
Ophthalmology Examination		X	X
Neurological Examination [d]		X	X
Developmental Assessments [e, f]		X [e]	X [e, f]
Review Diary (adverse events)		X	X
Adverse Events		X----------	----------X
Review of Ongoing Medications		X----------	----------X

a. Performed by patient's legal representative, at screening for Part A.
b. Include weight and head circumference.
c. Physiological tests and Behavioral tests
d. Neurological exam based on the Hammersmith Infant Neurological Examination.
e. Based on the Bayley Scales of Infant and Toddler Development (3rd Edition) .
f. Based on the Social Emotional and Adaptive-Behavior questionnaire from Bayley III – at Long-Term Follow-Up Visit 2 only

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1. INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) is the term given to a condition in which the normal pulmonary hypertension of the fetus is sustained after birth, and can complicate neonatal respiratory failure. PPHN is diagnosed in 1.9 per 1000 live births.[2] Mortality for PPHN is between 5-10% even with appropriate therapy,[3] and can be higher than 20%. Prevalence and mortality rates vary between centers and locales. Survivors have high morbidity in the forms of neurodevelopmental and audiological impairment, cognitive delays, and hearing loss.[4, 5]

PPHN is a complex syndrome, in which the cause is frequently unknown. The syndrome includes pulmonary vasoconstriction, right-to-left shunting through the ductus arteriosus and/or foramen ovale, and severe hypoxemia without evidence of congenital heart disease. The diverse underlying pathophysiologies of PPHN present early as hypoxic respiratory failure that is not responsive to 100% oxygen.

Newborns with hypoxic respiratory failure not controlled by comprehensive supportive intensive care measures (eg, mechanical ventilation techniques, surfactant administration, alkalinization, sedation, and neuromuscular blockade) are typically treated with inhaled nitric oxide (iNO). When inhaled, nitric oxide selectively dilates the pulmonary vasculature, with minimal effect on the systemic vasculature. Inhaled NO appears to increase the partial pressure of arterial oxygen (PaO_2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from lung regions with low ventilation/perfusion ratios toward regions with normal ratios. It is the only selective pulmonary vasodilator that has been shown to improve oxygenation in newborns with hypoxic respiratory failure.[6]

When iNO is not effective, patients may be maintained with extracorporeal membrane oxygenation (ECMO), which provides pump support for the dysfunctional heart and oxygenation for the failing lungs, while the pulmonary hypertension returns to expected post-natal levels. ECMO has been described as the most invasive therapeutic modality and the ultimate rescue.[7] Hypoxic respiratory failure is the most common reason for referral for neonatal ECMO.[8]

The Neonatal Inhaled Nitric Oxide Study Group (NINOS)[1] and Clinical Inhaled Nitric Oxide Research Group (CINRGI)[9] trials showed that treatment with iNO significantly reduces the need for ECMO in patients with hypoxic respiratory failure and/or PPHN. Despite this therapeutic benefit, in the NINOS and CINRGI trials, 39% and 38% of the subjects who received iNO, respectively, were eventually treated with ECMO because iNO had failed to correct their hypoxic respiratory failure. Recent data show the survival rate for newborns with PPHN who require ECMO is no more than 80%.[10] These data indicate that there remains a need for additional effective treatment options for this patient population.

Subsequent to NINOS and CINRGI and the widespread availability of iNO, it has become routine in many neonatal centers to treat hypoxic respiratory failure with iNO earlier, ie, in the presence of lesser degrees of hypoxemia, than it was initiated in NINOS and CINRGI (OI ≥25) and without clinical evidence of PPHN.

1.1. Indication

Revatio® is a PDE5 inhibitor that is approved in oral form for the treatment of pulmonary arterial hypertension (PAH) in adults (globally) and children (in the EU). The intravenous preparation is approved globally for the treatment of PAH in adults. In this study, the IV preparation will be studied in the treatment of term and near-term neonates with the disease of persistent pulmonary hypertension of the newborn (PPHN) or hypoxic respiratory failure (HRF) and at risk for PPHN.

1.2. Background and Rationale

This study is being conducted as part of a Paediatric Investigation Plan required by the Paediatric Committee (PDCO) of the European Medicines Agency (EMA).

1.2.1. Study Rationale

Treatment with iNO has been shown to significantly reduce the need for extracorporeal membrane oxygenation (ECMO) and has become a standard of care for neonates with PPHN. However, around 40 % of neonates with PPHN fail to respond to iNO.[11]

Furthermore long term complications of iNO in neonates are unknown and serious adverse events of iNO, such as methaemoglobinaemia, oxidative injury, and effects on platelet function have been reported.[12] In addition, administration of iNO is by inhalation, requiring intubation and ventilatory support in the neonatal ICU, with their associated risks for co-morbidities, such as nosocomial infections and pneumothorax.

Despite the availability of iNO and ECMO in tertiary specialised centres, hypoxic respiratory failure and PPHN remain life threatening conditions. Thus, there is a need for additional therapies for PPHN that may supplement the use of iNO or ECMO, increase the rate of recovery, and reduce time on the ventilator and in the ICU.

In Part A, the primary endpoints of this study will assess the efficacy of IV sildenafil to reduce the amount of time needed on iNO, by comparing the time on iNO plus sildenafil to time on iNO plus placebo in subjects without treatment failure, and to reduce the treatment failure rate of standard therapy. Anecdotal reports indicate that sildenafil (oral preparation via nasogastric tube) is added to iNO treatment for several reasons, such as to prevent rebound,[13] to augment the efficacy of iNO,[14] and in cases when PPHN is refractory to iNO treatment.[15]

The study is designed to allow subjects to begin treatment with standard of care, followed by additional treatment with IV sildenafil during the acute phase of the disease, and allow for a rapid removal of iNO as measured by improvement in disease state. These endpoints have the potential to assess the clinical as well as practical benefits of sildenafil as measured by the reduction in the duration of iNO therapy and reduction in the rate of treatment failure seen with iNO therapy.

Part B of this study is designed to monitor the developmental progress, neurological development, and long term safety of subjects enrolled in the study. All subjects who received study treatment (sildenafil or placebo) will be eligible to participate in this long-term follow-up part of the study.

1.2.2. Revatio®

Sildenafil citrate is a selective inhibitor of phosphodiesterase type 5 (PDE5). Present throughout the body, PDE5 is found in high concentrations in the lungs. Inhibition of PDE5 enhances the vasodilatory effects of nitric oxide in pulmonary hypertension by preventing the degradation of cyclic guanosine monophosphate (cGMP), which promotes relaxation of vascular smooth muscle and increases blood flow.

Sildenafil produces a relatively selective reduction in pulmonary artery pressure without adverse systemic hemodynamic effects.

Revatio® (sildenafil citrate) has been licensed in adults for use in the treatment of pulmonary arterial hypertension (PAH); approval granted in 2005 in the EU and the US. In May 2011, the European Commission approved Revatio® for the treatment of paediatric patients aged 1 to 17 years with PAH. Also, there are reports that sildenafil may have utility in the treatment of neonates with PPHN.[14, 16, 17]

For further information on completed and ongoing studies conducted in support of this indication, refer to the Investigators' Brochure.

1.2.3. Previous Clinical Experience in PPHN

Study A1481157 was a seven day, open-label, multicentre study in 36 neonatal patients with PPHN or hypoxic respiratory failure and at risk of developing PPHN. The study consisted of eight escalating-dose groups (see Table 1) with patients receiving study drug for at least 48 hours and for up to 7 days with or without the addition of standard treatment.

Seven neonates were enrolled before treatment with iNO was started. In these neonates, OI improved after initiation of sildenafil infusion and 6 of the 7 neonates completed treatment without the need for iNO or ECMO. Twenty-nine subjects were on iNO prior to study start. Among these 29 subjects, 2 (7%) needed ECMO or died.

Sildenafil was given at increasing doses in this study. Twenty subjects had a total of 41 treatment emergent adverse events, and only five of these were regarded as related to study drug. There was one death and four serious treatment emergent adverse events, none were considered related to study treatment. In total, four neonates were withdrawn from the study due to treatment emergent adverse events, two of which were regarded as treatment related. The majority of adverse events were mild or moderate in severity. However, five treatment emergent events, reported in five neonate patients, were rated as severe (three of which were also recorded as serious adverse events). None of these were considered treatment related.

Study A1481276 was an open-label, single centre, single arm study to determine the efficacy of IV sildenafil as monotherapy in the treatment of neonatal patients (target 40 subjects) with PPHN or hypoxic respiratory failure and at risk of developing PPHN. The subjects were to be naïve to iNO treatment.

The study consisted of one dosing group, with all subjects receiving IV sildenafil for up to 14-days. Standard treatment – iNO and/or ECMO – could be provided for lack of efficacy, at the discretion of the investigator/treating physician. Sildenafil was given as a 30-minute loading dose, followed by a maintenance dose, according to the subject's weight (see Section 1.2.4 Dose Rationale).

Four subjects were enrolled into the study, and received IV sildenafil. One subject completed the study without the need for iNO or ECMO. Three subjects discontinued the study early. One subject was disqualified following echocardiogram results showing ductal shunting due to a patent ductus arteriosus (PDA). The second subject was discontinued from the study due to adverse event (Reduced cardiac function), and was treated with ECMO. The third subject did not respond to sildenafil or iNO and suffered worsening PPHN which led to her death.

Thirty-four treatment emergent adverse events were reported for the four subjects. None were considered as related to study treatment. Three of these AEs were reported, for two subjects, as serious AEs (bradycardia, congenital pneumonia, and worsening PPHN leading to death). None of these were considered treatment related.

Due to evolved standard of care and widespread use of iNO at early signs of hypoxic respiratory failure or PPHN, the clinical relevance of study A1481276 came into question. Dialogue with physicians and the Paediatric Committee (PDCO) of the European Medicines Agency (EMA) led to terminating study A1481276 and designing study A1481316 to address clinical benefit of IV sildenafil in the context of iNO treatment.

1.2.4. Dose Rationale

In Study A1481157, 36 near- and full-term neonates diagnosed with PPHN were administered intravenous sildenafil within 72 hours of birth. One patient died during the study from her underlying disease, and data from this patient were not included in the pharmacokinetic analysis. The dosing regimen consisted of a loading infusion of fixed duration ranging from 5 min to 3 hours among treatment groups, followed by a continuous maintenance infusion of variable duration, ranging from 2.5 to 168 hours for individual patients. All but 4 patients received the maintenance infusion for at least the minimum duration of 48 hours specified in the protocol. One group of four patients received the maintenance infusion only.

Table 1. Mean Rate and Duration of Intravenous Sildenafil Loading and Maintenance Infusions Administered to Neonates in Each Treatment (Dose) Group in Study A1481157 (Based on Approximate Body Weight of 3 kg)

Treatment group	Number of patients	Loading dose		Maintenance dose	
		Rate (mg/h)	Duration (h)	Rate (mg/h)	Duration (h)
1	2	0.47	0.06	0.01	62.9
2	4	0.07	0.51	0.01	87.9
3	4	0.18	0.50	0.02	108
4	6	0.37	0.50	0.06	72.1
5	5	0.86	0.50	0.12	56.7
6	6	1.75	0.59	0.22	60.4
7	5	NA	NA	0.22	66.0
8	4	0.48	3.00	0.22	90.1

NA, loading dose not administered
Source: CSR Table 10

PK and oxygenation index were measured in 35 of the 36 PPHN neonates enrolled in the study.

A population PK model was developed from the study which described the pharmacokinetics of sildenafil in PPHN patients.[18] Subsequently, an exploratory indirect response PK-PD model for oxygenation index (OI) was developed which adequately described the pharmacodynamics of OI. The established PK and PK-PD model combined with the observed PK and OI data indicated that a similar OI response was observed across all dose groups, and also predicted by the PK-PD model across all dose groups in Study A1481157, potentially any dose regimen tested could be taken forward in terms of OI response.

Since the link between OI and the reduced need for iNO is uncertain, the relationship of a response between sildenafil and iNO is unknown, and treatment failure is seriously detrimental for patients with this disease, the targeted dose regimen for this study should:

- Achieve the maximum OI response observed in Study A1481157.
- Achieve sufficient sildenafil exposure which has been shown to be efficacious in children/adults treated for PAH.

Part A

The proposed dose regimen for Part A of this study (A1481316) is a loading dose of 0.1 mg/kg given over 30 minutes followed by a maintenance dose of 0.03 mg/kg/h, is predicted to achieve these two targets. Using this regimen the sildenafil concentration at steady state is predicted to be [Mean (95% CI), 57(32, 98) ng/mL], similar to what has been shown to be efficacious in children/adults treated for PAH. This dosing regimen was utilized in Study A1481276; there were no reports of adverse events or tolerability issues related to IV sildenafil infusion.

Part B

Part B of this study is non-interventional. No study medication will be given.

Complete information for this compound may be found in the Single Reference Safety Document, which for this study is the Investigator's Brochure (IB) for Revatio®.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objectives

- The primary objectives of this study are to evaluate the efficacy and safety of IV sildenafil when added to iNO for the treatment of neonates with PPHN or hypoxic respiratory failure and at risk for PPHN.

2.1.2. Secondary Objectives

- To monitor the developmental progress of patients with PPHN treated with IV sildenafil or placebo, at 12 and 24 months after the end of study treatment.

- Pharmacokinetics (PK): To further characterize the PK of sildenafil and its major metabolite UK-103,320 in neonates with PPHN or HRF and at risk of developing PPHN.

2.2. Endpoints

This protocol will not use an independent endpoint adjudication committee.

2.2.1. Part A

2.2.1.1. Primary Endpoints

Assessed at Day 14 or hospital discharge, whichever occurs first:

- Time on iNO treatment after initiation of IV study drug for subjects without treatment failure;

And

- Treatment failure rate, defined as need for additional treatment targeting PPHN, need for ECMO, or death during the study.

2.2.1.2. Secondary Endpoints

Assessed at Day 14 or hospital discharge, whichever occurs first:

- Time to final weaning of mechanical ventilation for PPHN;

- Time from initiation of study drug to treatment failure (additional drug treatment targeting PPHN, ECMO, or death); each component will also be evaluated separately;
- Proportion of subjects with individual components of treatment failure (needing additional treatment targeting PPHN, needing ECMO, or who die);
- Change in OI at 6, 12, and 24 hours from baseline;
- Change in differential saturation (pre- and post-ductal) at 6, 12, and 24 hours from baseline;
- Change in P/F ratio at 6, 12, and 24 hours from baseline;
- Sildenafil and its major metabolite UK-103,320 plasma concentrations and the corresponding PK parameters obtained from a population PK analysis; and
- Safety parameters: Incidence and severity of adverse events and abnormal laboratory parameters.

2.2.1.3. CCI

CCI

CCI

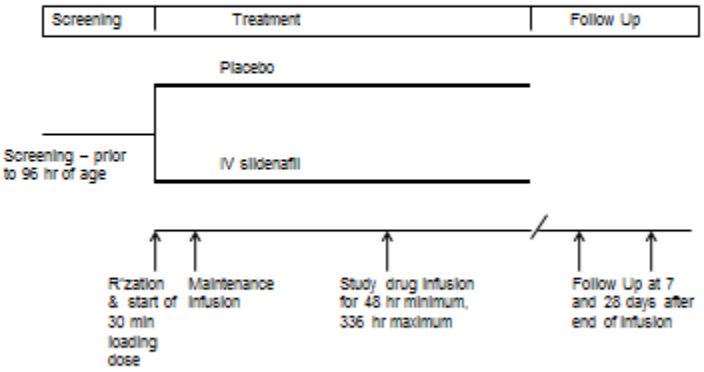
3. STUDY DESIGN

This study will be conducted in two parts. Part A is the double-blind phase and will be conducted during the acute phase of the disease, and consists of a screening phase, treatment phase, and follow-up phase. Part B is the long-term, non-interventional phase, and consists of two long-term follow-up visits at 12 and 24 months after the end of study drug infusion.

Analysis of the double-blind phase of the study (Part A) will be performed and a clinical study report will be written when all subjects have completed or discontinued from the double-blind phase. Analysis of the non-interventional phase of the study (Part B) will be performed when all subjects have completed or discontinued from the 2-year follow-up visit, and a final study report will be written.

Part A

Figure 1. Study Design Part A



This is the multi-center, multi-national, randomized, double-blind, placebo-controlled, parallel group part of the study with a screening phase, treatment phase, and follow-up phase. Neonates with PPHN or HRF and at risk for PPHN who are receiving iNO treatment will be evaluated for the study according to the inclusion/exclusion criteria, and randomly assigned to 1 of 2 blinded, parallel arms of study drug treatment: IV sildenafil or IV placebo (1:1 ratio; 32 subjects per group**).**

A 30-minute loading dose of study drug will be followed by the maintenance infusion. Should a serious or severe event of hypotension develop during the loading dose, per clinical judgment, the investigator has the option to reduce the infusion rate of the loading dose by 50%, or briefly stop the infusion for 15 minutes and then restart the loading dose at half the rate, for the rest of the loading dose.

Study drug infusion must continue for at least 48 hours, and may continue for up to 14-days, with or without the administration of additional therapy for PPHN, such as alternative pulmonary vasodilator. (See Section 5.5 Concomitant Medication for a list of prohibited medication.) **If maintaining study drug infusion for 48 hours is deemed by the investigator to compromise subject safety, the study drug infusion may be stopped, and the subject treated with standard care.**

Weaning from iNO, according to protocol-defined guidelines, must occur prior to stopping IV study drug, up to the 14-day infusion limit. After study drug discontinuation, the subject may be restarted within 24 hours if needed based on clinical decline, but not to exceed the 14-day infusion limit. All subjects will be followed up for medical status and adverse events at 7 and 28 days after the discontinuation of study drug.

Dosing instructions including a chart of infusion rates by weight will be provided to the study pharmacists. The study drug infusion will start with a loading dose of 0.1 mg/kg administered over 30 minutes. The loading dose is intended to bring the plasma concentration to the targeted level.

Part B

This long-term non-interventional phase of the study will evaluate the developmental progress of the subjects in the study at 12 and 24 months following the end of study treatment.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

If the study goal of 64 subjects enrolled is achieved after a potential subject's legal representative has signed the informed consent document, that subject will be allowed to enter the treatment phase and will be treated according to the protocol.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. PPHN, or hypoxic respiratory failure (HRF) at risk for PPHN associated with:
    - Idiopathic PPHN;
    - Meconium aspiration syndrome;

- Sepsis; or
- Pneumonia.

2. ≤96 hours of age at randomization (study medication must begin within 6 hours after randomization) and ≥34 weeks of gestation at screening.

3. OI >15 and <60, calculated using two blood gases taken at least 30 minutes apart prior to randomization.

4. Concurrent treatment with iNO at 10-20 ppm on ≥50% oxygen.

5. Screening echocardiogram, required before randomization if possible or within 24 hours of screening, to assess presence of pulmonary hypertension (defined as evidence of right to left shunting) and to eliminate subjects with large left to right intracardiac or ductal shunting.

6. Screening cranial ultrasound, required before randomization if possible or within 24 hours of screening, to eliminate subjects with clinically significant intracranial bleeds per investigator judgment.

7. Evidence of a personally signed and dated informed consent document indicating that the subject's legal representative has been informed of all pertinent aspects of the study; and

8. Subjects whose legal representative is willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Prior or immediate need for ECMO or CPR (defined as "full resuscitation outside the delivery room" including chest compression and medications such as adrenaline / epinephrine).

2. Expected duration of mechanical ventilation of less than 48 hours.

3. Life-threatening or lethal congenital anomaly.

4. Profound hypoxemia: PaO2 <30 mm Hg on any arterial blood gas drawn within 30 minutes of starting study drug infusion.

5. Severe hypotension or shock at baseline (mean arterial pressure (MAP) <30 mmHg) not responsive to medical management.

6. Significant congenital heart disease or defect exclusive of inter-atrial communication or patent ductus arteriosus.

7. Large left to right intracardiac or ductal shunting (diagnosed from echocardiogram taken before randomization if possible or within 24 hours of screening).

8. Large clinically significant intracranial bleed (diagnosed from cranial ultrasound taken before randomization if possible or within 24 hours of screening).

9. Lung hypoplasia syndromes diagnosed on the basis of prolonged oligohydramnios or hydrops faetalis.

10. Congenital diaphragmatic hernia.

11. Clinically significant active seizures, as per clinical judgment of the investigator.

12. Apgar score of <3 at 5 minutes after birth.

13. Bleeding diathesis, as per clinical judgment of the investigator.

14. Receipt of any prohibited concurrent medication/therapy at any time prior to screening:

    - Potent cytochrome P450 3A4 inhibitors (eg, erythromycin, ketoconazole, itraconazole, and protease inhibitors), erythromycin ophthalmic ointment is allowed;

    - Ritonavir or nicorandil;

    - Endothelin antagonists (eg, Tracleer®/bosentan, Letairis®/ambrisentan, etc);

    - PDE5 inhibitors (eg, sildenafil, tadalafil, vardenafil), IV or per orogastric tube;

    - Nitrates or nitric oxide donors, except iNO (A subject is eligible if nitroprusside was used only if it was discontinued at least 2 hours prior to study drug infusion; iNO may be used per protocol);

    - Vasodilators (eg, alpha blockers, magnesium sulfate as infusion, calcium channel blockers, other PDE inhibitors, prostacyclins, etc) at study entry (Excludes milrinone, which is allowed during the study as concurrent therapy) at study entry; or

    - Supplemental arginine administered for the purpose of improving NO-dependent vasodilation (Maintenance quantities in total parental nutrition (TPN) are allowed).

15. Known hereditary degenerative retinal disorders, such as retinitis pigmentosa.

16. Symptoms of drug- or alcohol-related withdrawal.

17. In the opinion of the investigator, a subject inappropriate for the study for any reason.

18. Other acute or severe medical conditions, or marked laboratory abnormalities that may increase the risk associated with study participation or investigational product administration, or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

19. Participation in any other experimental studies involving other drug or non-interventional therapies before the current study begins and/or during study participation.

20. Subjects who are relatives of investigational site staff members or Pfizer employees directly involved in the conduct of the trial.

4.3. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the trial is documented in the study contact list, located with study-related materials and manuals at each site.

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study number, contact information for the investigational site and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subjects participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the subject directly and if a subject calls that number they will be directed back to the investigational site.

5. STUDY TREATMENTS

This section applies only to Part A of the study.

This is a double-blind study in which the Sponsor’s study team, investigator and site staff, and subject’s legal representative are blinded. The investigator/site staff will enlist the aid of a research pharmacist(s) or other suitably qualified individual who is not directly involved in the care of study subjects, collecting study data or study assessments. At the beginning of the study, only active open-label supplies will be available. The site’s pharmacist(s) or other suitably qualified individual will be unblinded to study treatment and be involved in the receipt, storage, and preparation of the study drug / investigational product. In addition, they will maintain the blind with respect to all other study staff.

At the start of the study, unblinded open-label investigational product (sildenafil and empty placebo cartons) will be provided by the Sponsor, to the unblinded site pharmacist(s) or other suitably qualified individual at the site for storage and preparation.

When double-blind investigational product (active and placebo) are available, the supplies will be provided by the Sponsor to the site. The Sponsor's study team, investigator and site staff, and subject's legal representative are all blinded to the blinded investigational product (active and placebo)

5.1. Allocation to Treatment

The trial design uses 2 parallel arms with a ratio of 1:1, active treatment to placebo.

An automated IVRS will be utilized in this study. The system will assign randomization numbers to subjects, as they are determined to be eligible for study treatment, in accordance with the inclusion and exclusion criteria. The randomization number for each subject must be recorded in the appropriate case report form (CRF).

The site pharmacist(s) or other suitably qualified individual will receive the randomization treatment assignment with each unique randomization number. The site pharmacist(s) or other suitably qualified individual will prepare and label the investigational product for the loading dose and maintenance infusion according to the dilution instructions for the assigned randomization number and treatment type. All study staff, other than the site pharmacist(s) or other suitably qualified individual, will be blinded to study treatment

5.2. Breaking the Blind – for Blinded and Unblinded Investigational Product

The study will be double-blinded, to the Sponsor's study team, to the investigator and site staff, and to the subject's legal representative.

Exception for unblinded investigational product: the site pharmacist or other suitably qualified individual who prepares the study infusion will be unblinded to treatment assignment.

For **blinded investigational product**, the site pharmacist or other suitably qualified individual who prepares the study infusion will be blinded to treatment assignment and must follow the instructions for breaking the blind.

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be either a manual or electronic process. Blinding codes should only be broken in emergency situations for reasons of subject safety and in emergency situations *only if knowledge of the investigational product will alter the course of treatment of the subject.* Whenever possible, the investigator or sub-investigator consults with a member of the Sponsor's study team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the CRF.

If a subject's code is broken, the subject will continue to be followed up throughout the study as per the visit schedule.

When blinding codes must be broken for administrative reporting of SAEs to regulatory authorities, investigators, their site staff, and Pfizer staff involved in study conduct will remain blinded to treatment assignment unless necessary for patient management and/or proper treatment.

5.3. Investigational Product Supplies

5.3.1. Formulation and Packaging

5.3.1.1. For Unblinded Investigational Product

The active sildenafil investigational product will be provided to the site by the Sponsor. The investigational product sildenafil citrate 0.8 mg/mL solution for injection is presented in a single use 20 mL vial with an extractable volume of 12.5 mL. This solution must be diluted before administration as detailed in the Dosage and Administration Instructions (DAI; provided under separate cover).

The site will provide the appropriate reconstitution diluents (0.9% normal saline or dextrose 5%) required for preparation and administration of the IV sildenafil infusion.

The site will provide the appropriate solution (0.9% normal saline or dextrose 10%) required for administration of the IV placebo solution.

Labeled empty placebo cartons will be provided to the sites in order to maintain the blind for investigational product distribution and for IVRS drug assignment activities.

Standard therapy – iNO – will not be provided by the Sponsor.

5.3.1.2. For Blinded Investigational Product

When the blinded investigational product is available, it will be provided to the site by the Sponsor. The blinded investigational product (sildenafil citrate or placebo) is presented in a single use vial as a 12.5 mL fill in a 20 mL vial. This solution must be diluted before administration as detailed in the DAI (provided under separate cover).

The site will provide the appropriate reconstitution diluents (0.9% normal saline or dextrose 5%) required for preparation and administration of the blinded investigational product infusion.

Standard therapy – iNO – will not be provided by the Sponsor.

5.3.2. Preparation and Dispensing for Blinded and Unblinded Investigational Product

5.3.2.1. For Unblinded Investigational Product

The site's pharmacist(s) or other suitably qualified individual will be supplied with preparation and dispensing instructions that include investigational product loading dose and maintenance infusion rates according to subject's weight. Instructions for the active and placebo are provided in the written DAI.

5.3.2.2. For Blinded Investigational Product

When the blinded investigational product is available, the investigator/site staff and pharmacist(s) will be supplied with preparation and dispensing instructions that investigational product loading dose and maintenance infusion rates according to subject's weight in the written DAI.

5.3.3. Administration

The investigational product should be infused via a dedicated intravenous line or separate port if using a multi-lumen catheter.

Study medication must begin within 6 hours after randomization.

5.3.3.1. For Unblinded Investigational Product

For subjects randomized to receive active investigational product: IV sildenafil citrate will be administered as a loading dose of 0.1 mg/kg given over 30 minutes. This will be followed by a maintenance treatment consisting of an intravenous infusion of 0.03 mg/kg/hr.

For subjects randomized to receive placebo: IV 0.9% normal saline or dextrose 10% will be administered at a rate similar to that used for the active investigational product infusion, based on subject's weight, starting with the 30-minute loading dose, followed by the maintenance treatment infusion rate.

5.3.3.2. For Blinded Investigational Product

When the blinded investigational product is available, subjects randomized to receive active investigational product: blinded IV sildenafil citrate will be administered as a loading dose of 0.1 mg/kg given over 30 minutes. This will be followed by a maintenance treatment consisting of an intravenous infusion of 0.03 mg/kg/hr.

For subjects randomized to receive placebo: blinded placebo will be administered at a rate similar to that used for the active investigational product infusion, based on subject's weight.

5.3.3.3. For Unblinded and Blinded Investigational Product

Should a serious or severe event of hypotension develop during the loading dose, per clinical judgment, the investigator has the option to reduce the infusion rate of the loading dose by 50%, or briefly stop the infusion for 15 minutes and then restart the loading dose at half the rate, for the rest of the loading dose.

The duration of the infusion will be determined by the need of the individual subject (see Sections 6.2.4 and 6.2.5), but will be reviewed at Day 7 if still ongoing, and will not continue past 14-days of infusion.

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error case report form (CRF) which is a specific version of the adverse event (AE) page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the adverse event (AE) page and, if applicable, any associated adverse event(s) are captured on an adverse event (AE) CRF page.

5.3.4. Permanent Discontinuation of Investigational Product

Investigational product will be permanently discontinued after 14-days for any patients who remain on treatment up until this time. Worsening of clinical condition (in the investigator's opinion) that might occur upon discontinuation of investigational product should be treated using standard therapies at the discretion of the investigator.

5.4. Drug Storage and Drug Accountability

The investigator, or the research pharmacist, will ensure that all investigational product is stored in a secure area, only accessible to authorized personnel, under recommended storage conditions and in accordance with applicable regulatory requirements. Investigational product supply must be stored separately from normal hospital stock.

Investigators and site staff are reminded to check temperatures daily and ensure that thermometers are working correctly as required for proper storage of investigational products. Any temperature excursions should be reported immediately.

At the end of the study, the Sponsor will provide instructions as to disposition of any unused investigational product. If the Sponsor authorizes destruction at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the Sponsor. Destruction must be adequately documented.

5.5. Concomitant Medication(s)

Medications taken before the initiation of study medication, and which will not be continuing during the study, will be documented as a prior medication. Medications taken before the initiation of study medication and which will be continuing during the study, and medications taken after the initiation of study medication will be documented as concomitant medications.

Any medications administered during the study must be recorded with indication, daily dose, and start and stop dates/times of administration.

5.6. Prohibited Medications

The following medications/therapies are not allowed before or during the study treatment administration:

- Potent cytochrome P450 3A4 inhibitors (eg, erythromycin, ketoconazole, itraconazole, and protease inhibitors).
- Ritonavir or nicorandil.
- Endothelin antagonists (eg, Tracleer®/bosentan, Letairis®/ambrisentan, etc).
- PDE5 inhibitors (eg, Sildenafil (other than study drug), tadalafil, vardenafil), IV or per orogastric tube.
- Nitrates or nitric oxide donors in any form. A patient is eligible if nitroprusside was used only if it was discontinued at least 2 hours prior to study drug infusion; iNO will be used per protocol.
- Vasodilators (eg, alpha blockers, magnesium sulfate as infusion, calcium channel blockers, other PDE inhibitors, prostacyclins, etc). This excludes milrinone which is allowed during the study as concurrent therapy.
- Supplemental arginine administered for the purpose of improving NO-dependent vasodilation. Maintenance quantities in total parental nutrition (TPN) are allowed.

5.7. Standard/Rescue Therapy

For purposes of the study, standard therapy is defined as iNO, and ECMO is considered rescue therapy. The use of additional drug therapies **specifically targeting PPHN** (see Section 5.8) will contribute to the determination of treatment failure.

Standard background therapy for this study is iNO and will not be supplied by the Sponsor. A decision to treat the subject with ECMO for worsening of clinical condition at any time during the study should be made at the discretion of the investigator.

5.8. Additional Drug Treatment Targeting PPHN

If the condition of study subjects does not improve or worsens after the start of study medication, and the subject, in the opinion of the investigator, would benefit from additional drug treatment (especially to avoid use of ECMO), the investigator should institute any treatment necessary to provide maximum care for the subject. The study drug infusion should be stopped, and the investigator should begin additional treatment. The subject should remain in the study for the purpose of collecting safety and follow-up data.

The use of additional drug therapies prohibited by the protocol specifically targeting PPHN (eg, PDE5 inhibitors, endothelin antagonists, prostacyclins (inhaled or IV), magnesium sulfate infusion, nitroprusside, and vasopressin) will be considered failure of study treatment.

6. STUDY PROCEDURES

Part A is a short term study, conducted in an acute care setting. The study consists of a screening phase, treatment phase during which study drug is intravenously infused, and a follow-up phase consisting of 2 study visits.

Part B is a long-term extension of the study, conducted in the clinic offices, and consists of 2 long-term follow-up study visits.

Part A

6.1. Screening Period

The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each potential subject's parent/legal representative, in accordance with the procedures described in Section 12.3 on Subject Information and Consent. Potential subjects will be screened within 96 hours of birth, to confirm that they meet selection criteria for the study.

Any evaluations made prior to consent for non-study related reasons may be used for the screening procedures if they are well-documented.

All subjects should have an arterial line in place and when possible the line should be in a post-ductal site.

Subjects who meet the inclusion and exclusion criteria for the study will receive a screening evaluation prior to randomization. The following procedures will be completed as part of screening and prior to randomization:

- Complete medical history.
- Complete history of all medications since birth, including dietary supplements.
- Physical examination.
- Record birth weight and head circumference.

- Monitoring of concurrent/standard therapy (iNO).
- Vital signs, including systolic and diastolic blood pressure (BP), heart rate (HR), respiratory rate (RR), and oxygen saturation, measured by transcutaneous pulse oximetry from post-ductal sites.
- Oxygenation assessments: Arterial blood gases, PaO_2 (partial pressure of oxygen in arterial blood), OI, differential saturation, FiO_2 (the concentration of inspired oxygen), P/F ratio (derived PaO_2/FiO_2 ratio), and mean airway pressure.
- Echocardiogram within 24 hours of screening (as soon as possible) to assess presence of pulmonary hypertension and to rule out exclusionary intracardiac lesions.
- Cranial ultrasound within 24 hours of screening (as soon as possible) to rule out clinically significant intracranial bleed.
- Blood tests for safety laboratory tests will be collected.

All results related to exclusion criteria must be evaluated prior to randomization with the exception of the echocardiogram and the cranial ultrasound. If these results cannot be obtained in a timely manner, the subject may be randomized to study treatment prior to the evaluation of these results. However, the subject must immediately be withdrawn from study treatment if test results received after randomization disqualify the subject from the study based on exclusion criteria.

$$*OI = \frac{\text{Mean Airway Pressure x } FiO_2}{PaO_2}$$

Two screening OIs calculated* from ABG taken at least 30 minutes apart and prior to randomization must meet the inclusion/exclusion criteria to proceed with the study. Study drug infusion should begin as soon as possible after the second OI measurement**. Study medication must begin within 6 hours after randomization.**

All subjects should have an arterial line in place and when possible the line should be in a post-ductal site.

6.1.1. Procedures for Just Prior to Randomization

- Vital signs (BP, HR, RR, O_2 saturation).
- Ongoing review/recording of concomitant medications and background iNO therapy.
- Ongoing monitoring of adverse events.
- Blood sample for PK analysis. (Exception: study subjects in France).

[redacted]

- Randomization (assignment to blinded study therapy).
- Begin loading dose.

6.2. Treatment Period

Dosing instructions including a chart of infusion rates by weight will be provided to the study pharmacist. The study drug infusion will start with a loading dose (sildenafil or placebo) administered over 30 minutes, followed by the maintenance dose (sildenafil or placebo) administered at a lower infusion rate. **The study drug should be infused via a dedicated intravenous line or separate port if using a multi-lumen catheter**.

6.2.1. Procedures for Initial 30 Minutes of Study Treatment (Loading Dose)

- Administer loading dose for 30 minutes. Should a serious or severe event of hypotension develop during the loading dose, per clinical judgment, the investigator has the option to reduce the infusion rate of the loading dose by 50%, or briefly stop the infusion for 15 minutes and then restart the loading dose at half the rate, for the rest of the loading dose.
- Close monitoring of vital signs (BP, HR, RR, O_2 saturation); record vital signs every 15 minutes x 2.
- Ongoing review/recording of concomitant medications and background iNO therapy.
- Ongoing monitoring of adverse events.

6.2.2. Procedures for Maintenance Infusion Period

Study drug infusion must continue for at least 48 hours and may continue for up to 14-days (336 hours). If maintaining study drug infusion for 48 hours is deemed by the investigator to compromise subject safety, the study drug infusion may be stopped, and the subject treated with standard care.

- Reduce study drug infusion to maintenance infusion rate; infuse for at least 48 hours.
- Vital signs (BP, HR, RR, O_2 saturation) every 15 minutes x 2, every 30 minutes x 3 hours, at 12 hours from start of study drug infusion, then every 12 hours.
- Ongoing review/recording of concomitant medications and background iNO therapy.
- Ongoing monitoring of adverse events.
- Oxygenation assessments: Arterial blood gases, PaO_2, OI, differential saturation, FiO_2 P/F ratio, and mean airway pressure, targeted at (or as close as possible to) 1, 2, 6, and 12 hours after start of infusion – plus every 12 hours thereafter until the end of infusion whenever clinical samples coincide with these target time points.

- Blood samples for safety lab parameters once daily x 3 days, then every 48 hours until the end of infusion, plus as clinical need.

- Blood samples for PK analysis at 5 and 30 minutes (as close as possible, where practically possible) after the end of loading dose infusion; between 48 to 72, 96 to 120 hours during infusion. (Exception: study subjects in France).

6.2.3. Procedures for Weaning from iNO

If the subject is receiving iNO at >20 ppm, the investigator should make every attempt to decrease the iNO down to 20 ppm as soon as possible over 24 hours, according to site practice. As oxygenation improves, the FiO_2 should be decreased to 60%.

Weaning of iNO for study purposes should begin when the following conditions occur:

- iNO treatment is ≤20 ppm; AND

- FiO_2 ≤60%; AND

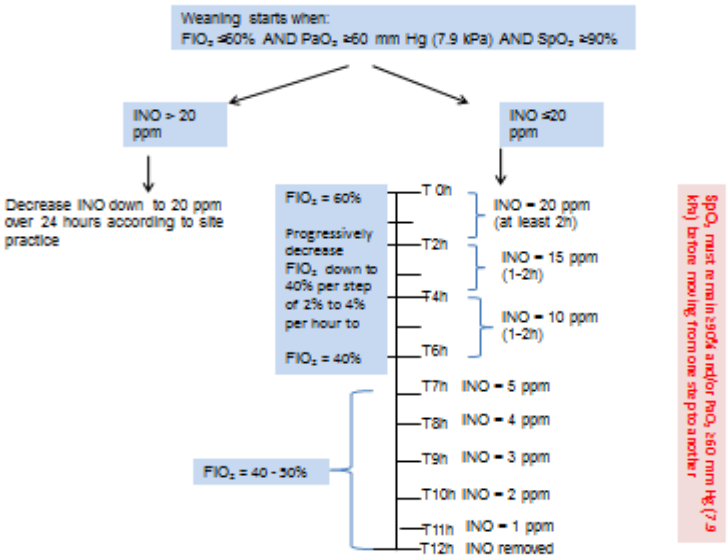
- PaO_2 ≥60 mm Hg (7.9 kPa); AND/OR

- SpO_2 (oxygen saturation per pulse oximeter) ≥90%.

The iNO should be decreased to 5 ppm by decrements of 5 ppm every 1-2 hours. At the same time, the FiO_2 should be decreased by steps of 2% to 4% per hour to 40%. After that, iNO should be weaned by 1 ppm every 1-2 hours down to 0 ppm. During this time, the subject's oxygen saturation should be monitored closely, and the FiO_2 may be increased as needed. PaO_2 must remain ≥60 mm Hg and/or SpO_2 ≥90% before moving from one step to the next. See Figure 2 below for an illustrated representation of possible weaning scenario.

If the subject's oxygen saturation decreases at any time during the weaning process, the investigator should increase iNO and FiO_2 as needed, and try weaning again when the subject is stable.

Figure 2. Weaning from iNO - Illustration



6.2.4. Stopping Study Drug Infusion (Between 48 and 336 hours)

Study drug infusion may be discontinued at anytime during the study, if the infusion is deemed by the investigator to compromise subject safety and well-being. The subject will be treated with standard care.

After a minimum treatment period of 48 hours, and ***after*** iNO treatment has been successfully weaned off, study drug infusion may be discontinued at the investigator's discretion, according to the following steps:

- The iNO treatment must be discontinued at least 1 hour prior to discontinuation of study drug, unless the 14-day infusion limit (336 hours) has been reached.
- If PaO_2 ≥60 mm Hg (or 7.9 kPa) and/or SpO_2 ≥90% and FiO_2 is 40-50%, the rate of study drug infusion will be reduced by half and the infusion continued for 12 hours (±1 hour).
- If PaO_2 ≥60 mm Hg (or 7.9 kPa) and/or SpO_2 ≥90% and FiO_2 is 40-50% after 12 (±1) hours, the study drug infusion will be discontinued.
- The date, time, and rate of study drug infusion changes should be recorded in the CRF.

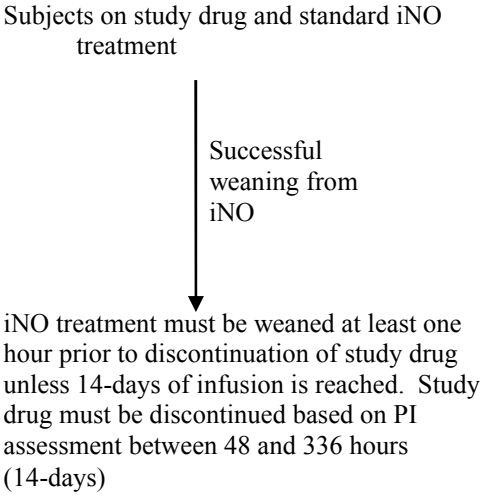
- If the end of the 14-day infusion limit has been reached, iNO therapy does not need to be discontinued prior to or at the time of study drug discontinuation (Figure 3).

- Oxygenation will be monitored as often as clinically necessary after discontinuation of study drug.

- If PaO_2 ≥60 mm Hg (or 7.9 kPa) and/or SpO_2 ≥90% can be maintained after discontinuation of study drug without increasing FiO_2 by >0.15 (relative increase, for example, an increase of 40% to 46%), study drug and/or iNO should not be restarted.

- Supplemental oxygenation and ventilator support may continue.

Figure 3. Stopping Study Drug Infusion (Between 48 and 336 Hours)



6.2.5. Restarting Study Drug Infusion

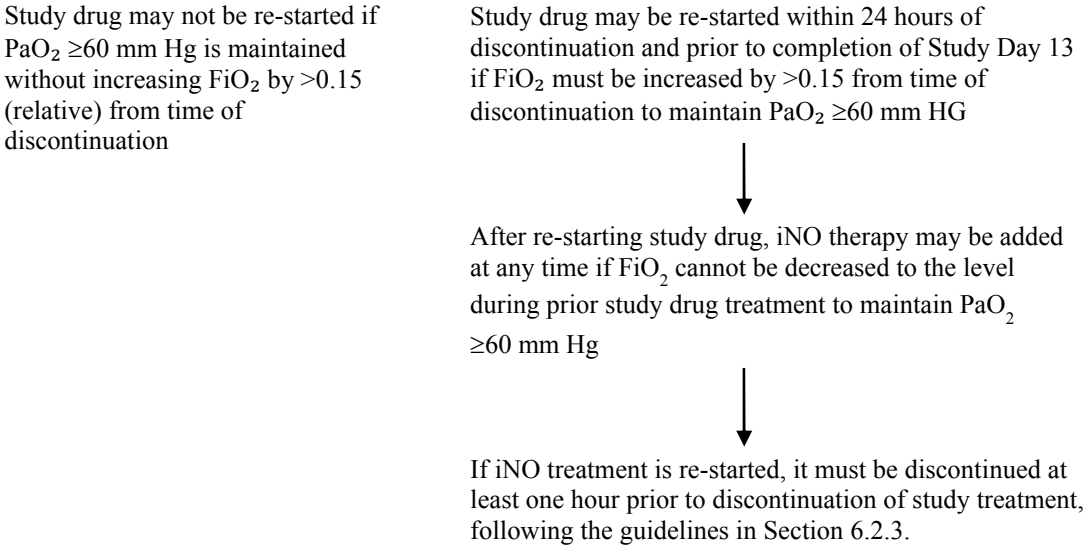
If FiO_2 must be increased by >0.15 (relative increase, for example, an increase of 40% to 46%) following study drug discontinuation to maintain PaO_2 ≥60 mm Hg and/or SpO_2 ≥90%, study drug infusion may be re-started at the maintenance infusion rate at any time within 24 hours of discontinuation and prior to the completion of Study Day 13. After re-starting study drug, iNO therapy may be added at any time if FiO_2 cannot be decreased to the level maintained during prior study drug treatment to maintain PaO_2 ≥60 mm Hg and/or SpO_2 ≥90%. Again, if iNO treatment is re-started, it must be discontinued at least one hour prior to discontinuation of study treatment, following the guidelines in Section 6.2.3 and 6.2.4 above.

Each time the study drug infusion is re-started, the following assessments should be taken and recorded in the CRF:

- Oxygenation assessments (PaO_2, FiO_2, and mean airway pressure) prior to study drug re-start, every 12 hours during study drug infusion, prior to the end of infusion.

- Vital signs (BP, HR, RR, O_2 saturation) at the time of re-start, every 12 hours during study drug infusion, and just after the end of infusion.

Figure 4. Restarting Study Drug Infusion



6.2.6. Permanent Discontinuation of Study Drug Infusion after 336 hours

Study drug infusion will be permanently discontinued after 14-days (336 hours) in all subjects remaining on study drug. Worsening of clinical condition (in the investigator's opinion) that might occur upon discontinuation of study drug should be treated using standard therapies, at the discretion of the investigator.

6.2.7. Procedures for End of Study Drug Treatment (≤14-Days)

At the time of study drug discontinuation, the following assessments should be taken and recorded in the CRF:

- Blood sample for PK analysis immediately **prior to end of infusion**; within 4 to 8, 18-24, and 40 to 48 hours after end of study drug infusion. (Exception: study subjects in France).
- Vital signs (BP, HR, RR, O_2 saturation).
- Ongoing review/recording of concomitant medications and background iNO therapy.
- Ongoing monitoring of adverse events.
- Oxygenation assessments: Arterial blood gases, PaO_2, OI, differential saturation, FiO_2 P/F ratio, and mean airway pressure.
- Blood samples for safety laboratory parameters.

NOTE: If the study drug infusion is stopped and then restarted, the vital signs and all other assessments must be repeated after subsequent discontinuations; however, the physical exam and safety laboratory sampling will not be repeated.

6.3. Follow-up Visits (short-term)

There will be two short-term follow-up visits for this study: Follow Up 1 and Follow Up 2 will be conducted at 7±3 days (or hospital discharge if sooner) and 28±3 days, respectively, **after the end of the study drug infusion**. Follow Up 2 visit may be conducted as a telephone call instead of a clinic or office visit.

Assessments will be conducted as follows:

- Follow Up 1 (or hospital discharge if sooner):
    - Vital signs (BP, HR, RR, O_2 saturation);
    - Physical examination;
    - Monitoring of adverse events;
    - Monitoring of concomitant medications, if subject remains hospitalized;
    - Dispense diary for the recording of possible adverse events until the next study visit.

At Part A Follow-up Visit 1, the subject's parent/legal representative will be given a diary for the recording of possible adverse events between visits. The investigator will instruct the parent/legal representative to collect possible adverse events until the next study visit.

- Follow Up 2 (may be conducted as a telephone call):
    - Monitoring of adverse events;
    - Monitoring of concomitant medications, if subject remains hospitalized;
    - If conducted in person, dispense diary for the recording of possible adverse events until the next study visit.

Part B

6.4. Long-Term Follow-up Visits

There will be two long-term follow-up visits for this study. Long-term Follow-Up Visit 1 will be conducted 12 (±2) months following the end of study drug infusion. Long-term Follow-Up Visit 2 will be conducted 24 (±2) months following the end of study drug infusion. The following procedures will be completed at each visit:

- Record medical history, including any hospital admissions since discharge from Part A.
- Physical examination.
- Review and record any medications that are considered by the investigator to be clinically significant.
- Audiological evaluations (physiological tests and behavioral tests).
- Ophthalmology examination for visual acuity.
- Neurological examination.
- Development assessments.
- Record any adverse events.

At each Part B study visit, the investigator will review the diary with the parent/legal representative, assess the clinical significance of these events, and record as new entries for Medical History, SAEs, or AEs. A new diary will be provided to the parent/legal representative at the end of Part B Visit 1, to be returned at Part B Visit 2.

NOTE: In consideration of the need to schedule and conduct Part B visit procedures in multiple clinics, involving multiple specialists, and to reduce the burden on study subjects of multiple assessments, the Long-Term Visit procedures may be conducted on separate days as needed. All procedures must be performed within the Study Visit windows of 12 and 24 (±2) months following the end of study drug infusion, as noted above.

6.5. Subject Withdrawal

Subjects may be withdrawn from the study at any time at the request of their legal representative, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject or legal representative to comply with the protocol required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject's legal representative. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events (AEs).

If the subject is withdrawn from the study, and the legal representative also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, which may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well being of the subject. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Blood Volume

Blood samples will be taken for safety, oxygenation assessments, and PK analysis. Whenever possible, the actual times of blood sampling may coincide with the collection of clinical samples. Additional study blood samples may be taken provided the total volume taken for the study does not exceed 10 mL.

NOTE: Blood samples for PK analysis will not be taken from study subjects in France.

7.2. Safety

7.2.1. Laboratory

The following safety laboratory tests will be performed at screening, once daily for 3 days, and then every 48 hours thereafter until the end of the study infusion and as per clinical need. Whenever possible, laboratory tests for the study should be made to coincide with clinical need.

Hematology	Chemistry
Hemoglobin Hematocrit RBC count Platelet count WBC count Total	Urea Creatinine Calcium Sodium Potassium Chloride Total CO2 (Bicarbonate) AST or ALT (depending on practice)* Total Bilirubin*

*If results are abnormal for subject's age, a liver function panel (including AST, ALT, total bilirubin, conjugated bilirubin, alkaline phosphatase, total protein) should be measured.

7.2.2. Adverse Events

Adverse events will be monitored from the time the subject's legal representative provides informed consent through and including Long Term Follow Up Visit 2. See Section 8 Adverse Event Reporting for detailed information.

7.3. Vital Signs

Vital sign assessments are: systolic and diastolic blood pressure (BP), heart rate (HR), respiratory rate (RR), and oxygen saturation (SO_2).

Vital signs will be recorded in the study CRF at the following target times, or as close to these times as possible:

- Screening.
- Randomization, just prior to start of study drug infusion.
- Every 15 minutes for the first hour, every 30 minutes for the next 3 hours, at 12 hours after the initiation of study infusion, every 12 hours thereafter until the end of study infusion, and at the end of the infusion.
- At Part A Follow-Up Visit 1, or hospital discharge, whichever occurs first.

NOTE: If the study drug infusion is stopped and then restarted, the vital signs must be taken at the time of re-start, every 12 hours during study drug infusion, and just after the end of infusion, and recorded in the CRF.

7.4. Physical Examination, Head Circumference, Weight

A physical examination will be performed by trained medical personnel at the investigator site at Screening, at Follow-up Visit 1 / hospital discharge, and at both Long-term Follow-Up visits in Part B. Clinically significant changes, in the judgment of the investigator, will be recorded as adverse events.

The following parameters will be assessed, *to the extent possible*:

- General appearance.
- Birth weight and head circumference.
- Respiratory system.
- Skin examination for the presence of abnormality.
- Abdominal examination for the presence of abnormalities.
- Neurologic examination to record the presence of abnormalities in motor and sensory function, to the extent possible. If the subject is paralyzed and sedated, record such in the case report form.
- Eye examination including pupillary response.
- Any additional assessments needed to establish status or evaluate symptoms or adverse experiences.

7.5. Development Progress Assessments

For Part B of the study, the following assessments will be performed:

Neurological examinations are to be performed by a physician (such as investigator, pediatrician, neurologist, neonatologist, etc.), with a score based on the Hammersmith Infant Neurological Examination (also known as Neurology Optimality Score)[19].

Developmental assessments to be performed by a Developmental Therapist:

- Bayley Scales of Infant and Toddler Development (3rd edition) scores on cognition, expressive and comprehensive language, fine and gross motor development.[20]

- Analysis of the results of the Social Emotional and Adaptive-Behavior questionnaire from Bayley III, completed by the parents[20] – for the Long-term Follow-Up Visit 2 (2-year) only.

Audiological evaluations are to be conducted by an audiologist and will include physiological tests of auditory system function (ie, tympanometry, acoustic reflex, and otoacoustic emissions (OAE)) and behavioral tests of hearing sensitivity (ie, visual reinforcement audiometry (VRA)) using developmentally appropriate methods suited to the individual patient and standardized criteria for the identification of auditory system dysfunction and hearing loss. (see Appendix 2 for details).

Orthoptic assessment/ophthalmological review are to be conducted by a qualified ophthalmologist/optometrist:

- A general eye examination, looking for the presence of amblyopia, strabismus, nystagmus.

- Acuity will be assessed using Teller cards and fix and follow.

- Pupil response will be examined. The pupils will be dilated and the fundus will be examined and any abnormalities noted.

- Refraction will be measured.

In the case of any abnormal observation, the ophthalmologist conducting the examination will attempt to obtain an image

7.6. Echocardiogram

Echocardiograms will be conducted according to the site's local procedures to assess diagnosis of PPHN (presence of right to left shunting) and any morphological changes which may exclude subjects (eg, large left to right intracardiac or ductal shunting).

- Before randomization if possible or within 24 hours of screening.

7.7. Cranial Ultrasound

Cranial ultrasound will be assessed according to the site's local procedures to exclude subjects who may have a clinically significant intracranial bleed, in the opinion of the investigator.

- Before randomization if possible or within 24 hours of screening.

7.8. Study Oxygenation Assessments

Study oxygenation assessments will be recorded in the study CRF whenever clinical samples coincide at the following targeted times, or as close to these times as possible.

- Screening.
- 1, 2, 6, and 12 hours after initiation of the study infusion plus every 12 hours thereafter until the end of the study infusion.

Assessments included are as follows:

- Arterial blood gases, PaO_2 (Partial Pressure of Oxygen in Arterial Blood).
- Oxygenation index (OI).
- Differential saturation.
- FiO_2.
- Derived (PaO_2/FiO_2) ratio.
- Mean airway pressure.

OI will be calculated twice at screening, at least 30 minutes apart, to assess inclusion eligibility.

7.9. Pharmacokinetics

NOTE: This section is not applicable for study subjects in France.

During the study, blood samples (0.3 mL) to provide a minimum of 0.1 mL plasma for pharmacokinetic analysis will be collected into appropriately labeled tubes containing lithium heparin at the following target collection times, where practically possible, as close to the target times as possible:

- Prior to dosing.
- At 5 and 30 minutes after the end of the loading infusion.
- Within 48-72 hours and within 96-120 hours of the continuous maintenance infusion.

- Prior to the end of the continuous maintenance infusion.
- Where practically possible within 4-8 hours after the end of the continuous maintenance infusion.
- Where practically possible within 18-24 hours after the end of the continuous maintenance infusion.
- Where practically possible within 40-48 hours after the end of the continuous maintenance infusion.

If treatment is stopped at any point prior to the 48 to 120 hour PK samples, a PK sample will be taken immediately prior to the end of the infusion and if practical the post infusion PK samples will be collected as scheduled.

If the infusion is re-started, and only one post-infusion PK blood sample has been collected previously, a sample will be drawn prior to re-starting. Subsequent samples are not required.

An interim analysis will be performed by an unblinded PK analyst after a minimum of 10 subjects in Part A have completed the study. Observed sildenafil concentration-time data will be evaluated to determine whether PK sampling should occur during all three proposed sampling windows (4-8 hrs; 18-24 hrs; and 40-48 hrs) following the stop of infusion. **If all samples within a given window are below the lower limit of quantification, the PK sample collection in its associated window may be dropped for subsequent subjects. If this change is deemed appropriate, the Pfizer study team will communicate this change to the study sites in writing.**

- Blood samples must not be collected from the catheter or port connected to study drug infusion.
- Samples will be centrifuged at approximately 1700 x g for about 10 minutes at 4°C. The plasma will be stored in appropriately labeled screw-capped polypropylene tube at approximately -20°C within 6 hours of collection.
- Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.
- As part of understanding the pharmacokinetics of the study drug, samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report. Samples collected for this purpose will be retained in accordance to local regulations and if not used within this timeframe, will be destroyed.

7.9.1. Shipment of Pharmacokinetic Samples

The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the Case Report Form (CRF) from the time the subject has taken at least 1 dose of investigational product through the subject's last visit.

For the purposes of this study:

A diary will be given to the subject's parent/legal guardian at Part A Follow-up Visit 1, and at Part B Long Term Follow-up Visits 1 and 2. The parent/legal guardian will be instructed by the investigator to record information related to possible adverse events that may occur between visits.

Between Part A follow-up Visit 1 (Part A follow-up Visit 2 may be a telephone call) and Part B Visit 1 and between Part B Visit 1 and Visit 2, the subject's parent/legally acceptable representative will collect possible adverse events in a diary. At the study visits, the

investigator will review the diary with the parent/legal representative, and will document in the diary which items meet the definitions of adverse events (See Section 8.3 below) or medical history, and which items are not considered either.

Medical history will be considered conditions that were present at birth but not detected at the time of screening in Part A, such as congenital or chromosomal abnormalities, or occurred prior to study drug treatment, and will be recorded in the CRF under Medical History. Adverse events will be recorded in the CRF as such.

SAEs must be reported from the time the subject's parent/legal representative provides informed consent through Part B Long-term Follow-Up Visit 2 and at any time an investigator becomes aware.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy.(EDP);
- Exposure via breastfeeding;

[redacted]

- Medication error;
- Occupational exposure.

8.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.5. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

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 drug dependency or drug abuse.

8.5.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

8.5.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 X ULN or not available.

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:

    - For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

- Concurrent with

- For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least one time the upper limit of normal **or** if the value reaches ≥3 times the upper limit of normal (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel

history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.6. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);

- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.7. Severity Assessment

If required on the AE case report forms (CRFs), the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.8. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see the Section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.9. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on a Serious Adverse Event (SAE) report form and Exposure During Pregnancy (EDP) supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.10. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an adverse event.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a Case Report Form (CRF), however a copy of the completed SAE report form is maintained in the investigator site file.

8.11. Withdrawal Due to Adverse Events (See Also the Section 6.5 on Subject Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.12. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the legally acceptable representative of the study subject. In addition, the study subject's legally acceptable representative will be questioned about AEs.

8.13. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.13.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports, as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.13.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.13.3. Sponsor's Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

A detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan, which will be dated and maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

The primary statistical objective is to test for the superiority of iNO + sildenafil over iNO + placebo for time on iNO treatment after initiation of IV study drug treatment for subjects without treatment failures and for treatment failure rate.

Sample size for time on iNO for subjects without treatment failure is based on the PPD internal database (Feb 2012). In the PPD database, there were 101-patients treated with iNO alone who were not treatment failures and met the following entry criteria of this proposed study: age ≤96 hours, gestational age ≥34 weeks, PPHN patients, 15 < OI <60 at baseline. The mean (S.D.) time on iNO for those 101 patients was 3.4 (1.88) days. It will be clinically relevant if subjects receiving iNO + Sildenafil have a 50% reduction in the time on iNO (ie, 1.7 days).

Sample size calculation for the treatment failure rate is based on the product label for iNOmax® and the Pfizer PPHN study A1481157. According to the product label of iNOmax®, the proportion of subjects who needed ECMO or died was 46% in the NINOS study and 33% in the CINRGI study. Treatment failure rate of 40% for iNO alone is being used for sample size calculation for this study.

In Pfizer PPHN study A1481157, there were 29 subjects who were on iNO prior to study and had sildenafil added during the study. Among the 29 subjects, 2 (7%) needed ECMO or died. Treatment failure rate of 10% for iNO + sildenafil is being used for sample size calculation for this study.

Total of 64 subjects (32 for each arm) will be enrolled in the study. Assuming 40% treatment failure rate in the iNO alone arm and 10% failure rate in the iNO+sildenafil arm:

- Time on iNO for subjects without treatment failure: 19 (59%) subjects in iNO alone vs. 29 (91%) subjects in iNO+ sildenafil will provide 85% power to detect a mean difference of 1.7 days for time on iNO, assuming mean of 3.4 days for iNO alone and population standard deviation of 1.88 days, at significance level of 0.05 from a 2-sided two sample t-test.

- Treatment failure rate: 32 subjects in each treatment will provide 80% power to detect an absolute difference of 30% (40% vs. 10%) at significance level of 0.05 (2-sided).

9.2. Efficacy Analysis

The intent-to-treat population (ITT) will consist of all randomized patients treated with study treatment. Per-protocol population (PP) will consist of all randomized patients who complete the study according to the protocol without any major violations. The primary efficacy analysis will be conducted using ITT population. If PP population is <90% of the ITT population, then efficacy analyses will also be conducted using PP population as sensitivity analyses.

Efficacy analysis will only be conducted for Part A of the study.

Analysis of the double-blind phase of the study (Part A) will be performed when all subjects have completed or discontinued from the double-blind phase, and a study report will be written. Analysis of the non-interventional phase of the study (Part B) will be performed when all subjects have completed or discontinued from the 2-year follow-up visit, and a final study report will be written.

9.2.1. Analysis of Co-Primary Endpoint

Time on iNO for subjects without treatment failures will be summarized for each treatment. If multiple iNO treatments are given to a subject, total time on iNO will be calculated for this endpoint for that subject. Treatment comparison will be conducted using analysis of covariance (ANCOVA) adjusting for time on iNO treatment prior to randomization. Mean treatment difference, its 95% confidence interval and p-value will be calculated.

Treatment failure rate and its 95% confidence interval will be calculated for each treatment group. Treatment comparison will be conducted using either Chi-square test or Fisher's exact test whichever is appropriate. Estimated treatment difference in rates, its 95% confidence interval and p-value will be calculated.

As the study will be conducted while subjects are treated in the hospitals, the chance of having missing data on primary endpoint is minimal.

9.2.2. Analysis of Secondary and CCI

For continuous endpoints, similar analyses (ANCOVA) conducted for time on iNO or 2-sample t-test (no adjustment for baseline values) will be used.

For categorical endpoints, similar analyses conducted for treatment failure rate will be used.

CCI

9.3. Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Analyses

A previously developed population PK model for sildenafil and its major metabolite UK-103,320 in PPHN patients[18] will be applied to estimate the pharmacokinetic parameters, using the plasma concentration time data of sildenafil and UK-103,320. CCI

The PK concentration-time data will be reported as part of the clinical study report (CSR). CCI

9.4. Safety Analysis

Safety analyses will be carried out for the ITT population only for both Part A and Part B of the study. All adverse events will be coded and grouped by system organ class. The incidence of each treatment emergent adverse event will be tabulated by treatment. Tabulations by maximum severity and relationship to study treatment will also be included.

Vital signs and safety laboratory data will be explored through the use of standard presentations of descriptive statistics.

For Part B of the study, results from the neurologic and development assessments, audiological evaluations, and ophthalmology tests will be summarized by randomized groups and total. Great caution must be exercised when comparing data between the 2 randomized groups as Part B is non-interventional and unblinded and various medical interventions can be prescribed per investigator judgment.

9.5. Interim Analysis

A PK interim analysis is planned for this study (See Section 7.9). There is no interim analysis planned for the double-blind phase of this study.

9.6. Data Monitoring Committee (DMC)

This study will use an External Data Monitoring Committee (E-DMC).

The DMC will be responsible for ongoing monitoring of the efficacy and safety of subjects in the study according to the Charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

The DMC will be independent of the study team and will have no direct involvement in other aspects of the trial. The DMC will develop its own operation procedures in consultation with the sponsor which will be documented in the DMC charter.

Upon the completion of Part A of the study, the DMC will assess the need to continue to monitor the safety data collected from Part B of the study.

The DMC will operate to the following rules:

- The DMC will provide recommendations to the Pfizer project team.
- The DMC will review unblinded critical efficacy and safety data (adverse events, SAE reports).
- If the incidence and/or severity of adverse events are clinically unacceptable then the DMC may recommend the study be terminated or a different dose of sildenafil be used.
- If a significant modification to the study is recommended by the DMC based on blinded data, the DMC Chair will request a confidential discussion with a Pfizer representative who is not part of the study team.

Details of possible stopping rules and operating procedures will be outlined in the DMC charter.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator’s site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008 and 1996 versions).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Subject names, address, birth date (if required by local law and/or Ethics Committees), and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the trial subject. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The investigator must ensure that each study subject, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. Assent from the subject will not be sought, in addition to consent from the legal representative, due to subjects' neonatal age

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject's legal representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Subject Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures. In addition, investigators may inform their local communities of the initiation of the study at the time of clinical review meetings or professional gatherings.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient subjects have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application (CTA)) and ethics application in the

Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in all Participating Countries

End of Trial in all participating countries is defined as:

- Last Patient Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of UK-092,480 at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 24 hours. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of this study on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrial.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary Completion Date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer has no objection to publication by an Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, the Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

The Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The Investigator will, on request, remove any previously undisclosed Confidential Information (other than the study results themselves) before disclosure.

If the study is part of a multi-centre study, the Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the Investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16. REFERENCES

1. The Neonatal Inhaled Nitric Oxide Study Group (NINOS). Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. N Engl J Med 1997;336:597-604.

2. Walsh-Sukys MC, Tyson JE, et al. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: Practice variation and outcomes. Pediatrics 2000;105(1):14-20.

3. Steinhorn RH. Neonatal Pulmonary Hypertension. Pediatr Crit Care Med. 2010 March;11(2Suppl):S79-S84.

4. Konduri GG, Vohr B, et al. Early inhaled nitric oxide therapy for term and near-term newborn infants with hypoxic respiratory failure: Neurodevelopment follow-up. J Pediatr 2007;150:235-240.

5. The Neonatal Inhaled Nitric Oxide Study Group (NINOS) Inhaled nitric oxide in term and near-term infants: Neurodevelopmental follow-up of The Neonatal Inhaled Nitric Oxide Study Group (NINOS). J Pediatr 2000;136:611-617.

6. INOmax® Label. http://inomax.com/full-pi.

7. Somme S, Liu DC. New trends in extracorporeal membrane oxygenation in newborn pulmonary diseases. Artificial Organs 2001;25(8):633-637.

8. Finer NN, Sun JW, et al. Randomized, prospective study of low-dose versus high-dose inhaled nitric oxide in the neonate with hypoxic respiratory failure. Pediatrics 2001;108(4):949-955.

9. Clark RH, Kueser TJ, et al. Low dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. N Engl J Med 2000;342:469-474.

10. http://www.unboundmedicine.com/pedscentral/ub/view/5-Minute-Pediatric-Consult/145312/all/Persistent_pulmonary_hypertension_of_the_newborn__PPHN_.

11. INOmax® Label. http://inomax.com/full-pi.

12. Greene JH, Klinger JR, et al. The efficacy of inhaled nitric oxide in the treatment of acute respiratory distress syndrome. An evidence-based medicine approach. Crit Care Clin 1998;14(3):387-409.

13. Namachivayam P, Theilen U, et al. Sildenafil prevents rebound pulmonary hypertension after withdrawal of nitric oxide in children. Am J Resp Crit Care Med 2006;174;1042-1047.

14. Spillars J. PPHN: Is sildenafil the new nitric? A review of the literature. Advances in Neonatal Care 2010;10(2):69-74.

15. Shivananda S, Ahliwahlia L, et al. Variation in the management of persistent pulmonary hypertension of the newborn: A survey of physicians in Canada, Australia, and New Zealand. Am J Perinatol 2012; Apr 11. [PubMed:22495900].

16. Vargas-Origel AG, Gomez-Rodriguez G, et al. The use of sildenafil in persistent pulmonary hypertension of the newborn. Am J Perinatol 2010;27(3):225-230.

17. Baquero H, Soliz A, et al. Oral Sildenafil in infants with persistent pulmonary hypertension of the newborn: A pilot randomized blinded study. Pediatrics 2006;117:1077-1083.

18. Mukherjee A, Dombi T, et al. Population pharmacokinetics of Sildenafil in term neonates: Evidence of rapid maturation of metabolic clearance in the early postnatal period. Clin Pharm & Ther. 2009;85(1):56-63.

19. Haataja L, Mercuri E, et al. Optimality Score for the neurological examination of the infant at 12 and 18 months of age. J Pediatr. 1999 Aug; 135:153-161.

20. Bayley Scales for Infant and Toddler Development, 3rd edition. Pearson Editors 2005.

Appendix 1.

DRUG STORAGE INSTRUCTIONS

Investigational product must be stored between 15-25^{0}C under secure (locked) conditions. The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. Investigators and site staff are reminded to check and record temperatures daily and ensure that thermometers are working correctly as required for proper storage of investigational products. Temperature Monitoring procedures and equipment should include the monitoring of minimum and maximum temperatures for awareness of potential temperature excursions at times when site staff are not actively monitoring/recording temperatures. If an excursion does occur please immediately notify the clinical research associate (CRA) (unblinded CRA for unblinded investigational product and blinded CRA for blinded investigational product) to determine the impact of the excursion. The site should not use the supplies until a disposition is received from the CRA. The investigational product should continue to be stored in its appropriate location pending the disposition from Pfizer. If the materials are rejected, Pfizer will initiate a replacement shipment to the site.

It is preferable that investigational product is destroyed on-site following site documented standard operating procedure (SOP)/guidelines and according to local requirements. Destruction cannot take place before the CRA (unblinded CRA for unblinded investigational product and blinded CRA for blinded investigational product) performs reconciliation and has approved site destruction procedures.

Study drug related to a product complaint must not be destroyed locally unless approval is given.

[redacted]

Appendix 2.

AUDIOLOGICAL EVALUATION

Audiological evaluations are to be conducted by an audiologist and will include physiological tests of auditory system function and behavioral tests of hearing sensitivity using developmentally appropriate methods suited to the individual patient and standardized criteria for the identification of auditory system dysfunction and hearing loss. Unless otherwise specified, all tests should be completed in both ears using the following specified procedures when possible; however, adjustments should be made for children that are unable to condition to or tolerate these procedures as defined. All tests should be analyzed using the following criteria.

Physiological Tests

- Tympanometry: tympanic membrane mobility, middle ear pressure, ear canal volume.
- Acoustic (Stapedial) Reflex: middle ear function, CNVIII and CNVII function.
- Otoacoustic Emissions (OAE): cochlear outer hair cell function.

Behavioral Test

- Visual Reinforcement Audiometry (VRA): hearing sensitivity.

Procedures

- Tympanometry: Performed using 226Hertz (Hz) probe tone.
- Acoustic (Stapedial) Reflex: Performed using 226Hz probe tone and 500Hz, 1000Hz, and 2000Hz ipsilateral stimulus.
- Otoacoustic Emissions: Performed using distortion product evoked emissions (DPOAE) in the 2000-8000Hz region or transient evoked emissions (TEOAE) in the 1000-4000Hz region.
- Behavioral Audiometry (VRA): Performed using air conduction pure tone or warble tone stimuli at 0.5, 1.0, 2.0, 4.0 and 8.0 k Hz under insert/ head phones or at 0.5, 1.0, 2.0, and 4.0 k Hz in the soundfield and at 0.5, 1.0, 2.0, and 4.0 k Hz under bone conduction when indicated.

Criteria

- Tympanometry: Reported using the following criteria and classifications (Hunter and Shahnaz, 2013)

Definition	Classification
ECV= 0.5 to 1.2 cc; Ytm = ≥ 0.3 mmho; TPP = +25 to -75 daPa	Type A / Normal
ECV = 0.5-1.22 cc; Ytm = NP; TPP = NP	Type B / Abnormal/ Flat/ Reduced Compliance
ECV = 0.5 to 1.22 cc; Ytm = ≥ 0.3 mmho; TPP = < -75 daPa	Type C/ Abnormal/ Negative Pressure
ECV = 0.5 to 1.22 cc; Ytm = < 0.3 mmho; TPP = +25 to -75 daPa	Type As / Abnormal / Reduced Compliance
ECV = 0.5 to 1.22 cc; Ytm = > 1.03 mmho; TPP = +25 to -75 daPa	Type AD / Abnormal/ Hypermobile/ Hypercompliant

ECV = ear canal volume; daPa = dekapascal; mmho = millimho; TPP = tympanometric peak pressure; Ytm = static acoustic admittance;

- Acoustic (Stapedial) Reflex: ≥ 0.03 ml deflection; reported presence or absence at each frequency tested (Gelfand et al 1990)

- Otoacoustic Emissions: ≥ 6dB signal-to-noise ratio; reported presence or absence for each approximate F2 frequency region (eg, 2000Hz) tested (Gorga et al 1997)

- Behavioral Audiometry (VRA): Reported in decibel hearing level (dB HL) and using the following criteria and hearing loss classifications (modified, Clark 1981)

    - A significant change in hearing or hearing loss is defined as: > 20 dB threshold shift at one frequency, >10 dB shift at two consecutive test frequencies, and/or a threshold shift to "no response" at three consecutive test frequencies. Change must be confirmed by retest (ASHA 1994)

Definition	Classification
≤ 20 dB HL	Normal
21 - 40 dB HL	Mild
41 – 70 dB HL	Moderate
71 – 90 dB HL	Severe
≥ 90 dB HL or no response	Profound

REFERENCES

Gorga, M. P., Neely, S. T., Ohlrich, B., Hoover, B, Redner, J., and Peters, J. From Laboratory to Clinic: A Large Scale Study of Distortion Product Otoacoustic Emissions in Ears with Normal Hearing and Ears with Hearing Loss. Ear & Hearing 1997: 18(6):440-455.

Clark, J.G. (1981) Uses and abuses of hearing loss classification, ASHA 23: 493-500. Cited in: Harrell, R.W. (2002) Puretone evaluation. In J. Katz, ed. Handbook of Clinical Audiology, 5th Ed. Baltimore: Lippincott Williams & Wilkins.

Gelfand, S.A., Schwander T., & Silman S. Acoustic reflex thresholds in normal and cochlear-impaired ears: effects of no-response rates on 90th percentiles in a large sample. Journal of Speech and Hearing Disorders 1990: 55, 198-205.

Hunter, L.L. and Shahnaz, N. Handbook of Acoustic Immittance. (2013). Plural Publishing.

ASHA (1994) Guidelines for the Audiologic Management of Individuals Receiving Cochleotoxic Drug Therapy. **http://www.asha.org/policy/GL1994-00003.htm**

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