INHALED NITRIC OXIDE/INOPULSE DEVICE COMBINATION PRODUCT

PULSE-PAH-004

A PHASE 3, PLACEBO CONTROLLED, DOUBLE-BLIND, RANDOMIZED, CLINICAL STUDY TO DETERMINE EFFICACY, SAFETY AND TOLERABILITY OF PULSED, INHALED NITRIC OXIDE (iNO) VERSUS PLACEBO IN SYMPTOMATIC SUBJECTS WITH PULMONARY ARTERIAL HYPERTENSION (PAH): INOvation-1 (Part 1 and Part 2)

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STUDY CONTACT INFORMATION

Role in Study	[redacted]
Sponsor's Clinical Leads	
Sponsor's Medical Lead	
Drug and Device Safety and Surveillance	

PULSE-PAH-004 Amendment 3

INVESTIGATOR'S AGREEMENT AND SPONSOR'S SIGNATURE PAGE

I have read the attached protocol entitled "*A Phase 3, Placebo Controlled, Double-Blind, Randomized, Clinical Study To Determine Efficacy, Safety and Tolerability of Pulsed, Inhaled Nitric Oxide (iNO) Versus Placebo In Symptomatic Subjects With Pulmonary Arterial Hypertension (PAH): INOvation-1 (Part 1 and Part 2)*", and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization (ICH) Tripartite Guideline on Good Clinical Practice (GCP), the ethical principles stated in the latest version of the Declaration of Helsinki, ISO 14155 and the applicable local and international regulations, whichever provide the greater protection of the individual.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Sponsor, Bellerophon Pulse Technologies LLC.

_____ _____

Principal Investigator Date

Sponsor Statement

This study protocol was subject to critical review and has been approved by the following Sponsor representatives.

[redacted]

2. SYNOPSIS

Name of Sponsor/Company:
Bellerophon Pulse Technologies LLC

Name of Investigational Drug/Device Combination Product:
Inhaled Nitric Oxide (iNO) / INOpulse

Title of Study: A Phase 3, Placebo Controlled, Double-Blind, Randomized, Clinical Study to Determine the Efficacy, Safety and Tolerability of Pulsed, Inhaled Nitric Oxide (iNO) Versus Placebo in Symptomatic Subjects with Pulmonary Arterial Hypertension (PAH): INOvation-1 (Part 1 and Part 2)

Study center(s): Up to approximately 115

Principal Investigator: TBD

Investigators: TBD

Phase of development: 3

Study period (years):

Estimated date first subject enrolled Part 1 June 2016

Estimated date last subject enrolled: Part 1 Jan 2018

Duration of treatment:

Part 1

Blinded Treatment Period: Maximum of 18 weeks.

Estimated Completion Date: After the last subject completes 18 week assessments

Part 2

Open Label Extension Period: Subjects will be offered open label therapy when the subject completes 18 weeks of blinded drug therapy. All subjects must have completed all assessments in Part 1 and remain on blinded treatment until week 18 before proceeding to Part 2.

Estimated Completion Date: Open Label Treatment with iNO at 75 mcg/kg IBW/hr with the INOpulse delivery device will be available to subjects who completed Part 1 until the drug-device investigational product is approved and available as a marketed product or the Sponsor decides to discontinue development of iNO for PAH or the Sponsor decides to terminate the study.

Objectives:

Part 1 -Blinded Treatment Period:

Primary Objective:

To evaluate the efficacy of inhaled nitric oxide (iNO) on exercise using 6-minute walk distance (6MWD) in subjects with pulmonary arterial hypertension (PAH) currently receiving background PAH medication and LTOT.

Secondary Objectives:

1. To evaluate the time to clinical worsening (TTCW)
2. To evaluate change in World Health Organization (WHO) Functional Class

Safety Objectives:

1. To evaluate the safety and tolerability of iNO

Tertiary Objectives:

1. To evaluate changes in health-related quality of life using the Short Form-36 (SF-36) version 2 health survey
2. To evaluate the impact of iNO on pulmonary hemodynamics in a subset of subjects
3. To evaluate changes in right ventricular (RV) and left ventricular (LV) function as measured by echocardiography, in a subset of subjects
4. To evaluate changes in N-terminal of the prohormone brain natriuretic peptide (NT-proBNP)
5. To evaluate change in Borg dyspnea score immediately following 6-minute walk test (6MWT)
6. To evaluate change in 6MWD as related to degree of correlation between drug adherence and clinical efficacy measurement
7. To evaluate subjects with unsatisfactory clinical response
8. To evaluate the impact of iNO on frequency of heart-lung or lung transplantation, and deaths while awaiting transplantation
9. To evaluate the impact of iNO on medical resource utilization

Part 2 Open Label Period:

Primary Objective:

1. To Evaluate the long term safety and tolerability of iNO

Secondary Objective:

2. To Evaluate the change in exercise tolerance in subjects who switch from placebo to active therapy

Endpoints:

Part 1 Blinded Treatment Period:

Primary Endpoint: The efficacy of iNO as measured by the placebo-adjusted change in 6MWD from baseline to 18 weeks.

Secondary Endpoints:

1. TTCW: The time (in days) from start of treatment to first event (first day the event is noted), with iNO as compared to placebo, measured from baseline to 18 weeks. TTCW event is defined as any of the following:
    a. Death (all-cause mortality)
    b. Atrial septostomy
    c. Hospitalization due to worsening of PAH (adjudicated)
    d. Start of new specific PAH treatment (endothelin receptor antagonists [ERAs], phosphodiesterase type-5 [PDE-5] inhibitors or prostanoids), an increase in the dose of an ERA or PDE-5, increase in the dose or frequency of an inhaled prostanoids, or an increase in the dose of an intravenous or subcutaneous prostanoids by >10%.
    e. Decrease of >15% from baseline or > 30% compared with the last study related measurement in 6MWD and should be confirmed by a repeat measurement performed at least 14 days later

f. Worsening of WHO Functional Class (e.g., from Class II to Class III or IV, OR Class III to Class IV); and should be confirmed by a repeat assessment at least 14 days later

2. Change in WHO Functional Class, with iNO as compared to placebo, from baseline to 18 weeks.

Tertiary Endpoints:

1. Change in health-related quality of life (using SF-36 version 2 health survey), with iNO as compared to placebo, from baseline to 18 weeks
2. Change in pulmonary hemodynamics (i.e., cardiac output [CO], cardiac index [CI], mean pulmonary artery pressure [mPAP], mean pulmonary capillary wedge pressure [mPCWP], systolic pulmonary artery pressure [sPAP], diastolic pulmonary artery pressure [dPAP], pulmonary vascular resistance [PVR], and oxygen saturation by pulse oximeter [SpO_2], mixed venous O_2, and right atrial pressure [RAP]), measured by right heart catheterization (RHC), with iNO as compared to placebo, from baseline to 18 weeks, in a subset of subjects (approximately 50), at selected sites
3. Change in echocardiogram measurements right ventricular function (including right ventricular fractional area change, systolic pulmonary artery pressure [sPAP], tricuspid annular motion/tricuspid annular plane systolic excursion, tricuspid annular systolic velocity, and Tei index) and left ventricular function (including left ventricular ejection fraction [LVEF], LV size, and improvement in LV early diastolic relaxation velocity), with iNO as compared to placebo, from baseline to 18 weeks, in a subset of subjects (approximately 50), at selected sites
4. Change in NT-proBNP, with iNO as compared to placebo, from screening to 18 weeks
5. Change in Borg dyspnea score immediately following 6MWT, with iNO as compared to placebo, from baseline to 18 weeks
6. Change in 6MWD as related to degree of drug adherence, with iNO as compared to placebo, from baseline to 18 weeks
7. The number of subjects with unsatisfactory clinical response, with iNO compared to placebo, from baseline to 18 weeks. Defined as: WHO Functional Class III or IV symptoms with no improvement in 6MWD
8. Number of subjects undergoing heart-lung or lung transplantation, number of subjects listed for transplantation, and deaths while awaiting transplantation, from baseline to 18 weeks
9. Medical resource utilization, with iNO as compared to placebo, from baseline to 18 weeks

Safety Endpoints:

1. Incidence and severity of adverse events (AEs)
2. Incidence of device malfunction and/or device failure leading to an AE
3. Incidence of rebound pulmonary hypertension (PH)
4. Clinically significant changes in the following:
    a. Clinical laboratory tests
    b. Pulmonary function tests
    c. Vital signs

Part 2 Open Label Period:

Primary Endpoint:

1. The incidence of AEs and SAEs with long term therapy

Secondary Endpoint:

1. To evaluate the change in 6MWD in subjects who switch from placebo to active therapy at 4 months, 8 months and 12 months of therapy

Methodology:

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group design to determine the efficacy, safety and tolerability of pulsed iNO versus placebo in symptomatic subjects with PAH.

Part 1 Blinded Treatment Phase:

Subjects will be randomized (1:1) at Week 0 to placebo at a dose setting of 75 mcg/kg ideal body weight (IBW)/hr, or iNO at a dose setting of 75 mcg/kg IBW/hr.

Following randomization, subjects will enter a 2 week run-in period. Subjects randomized to placebo will receive placebo and subjects randomized to active NO will receive low dose iNO at 15 mcg/kg IBW/hr. Subjects who do not comply with the required usage of the investigational INOpulse delivery device (hereafter INOpulse device) for an average of 12 hours per day, or longer, during the Run-in period will be discontinued. Those who qualify will enter into Part 1, the blinded treatment period, in the cohort they were randomized to at Week 0. Randomization will be stratified for use of prostanoids at baseline.

Part 2 Open Label Period:

After subjects have completed 18 weeks of blinded drug therapy and all assessments in Part 1 , subjects will be offered open label treatment with iNO 75 mcg/kg IBW/hr.

Number of subjects (planned): 188

Number of sites: Up to approximately 115

Part 1 Blinded Treatment Period: Diagnosis and main criteria for inclusion and exclusion:

Inclusion criteria:

1. Signed Informed Consent Form (and assent as appropriate) prior to the initiation of any study mandated procedures or assessments
2. A confirmed diagnosis of PAH Group 1 who have either idiopathic PAH (IPAH), heritable PAH, drug and toxin-induced PAH, associated PAH (APAH) with connective tissue disease (CTD), APAH with congenital heart disease (unrepaired or repaired at least 1 year prior to Screening), APAH with human immunodeficiency virus (HIV), or APAH with portal hypertension
3. Subjects receiving at least one PAH specific therapy (ERA or PDE-5 inhibitor, or inhaled, subcutaneous, or intravenous prostacyclin or a prostacyclin analog) **with the same type of therapy for at least 3 months with stable dosing 4 weeks prior to Screening**. (Subjects should be receiving optimal therapy according to the disease severity)
4. Subjects using oxygen therapy by nasal cannula for at least 4 weeks prior to Screening
5. PAH diagnosis confirmed by RHC within the previous 5 years, according to the following definitions:
    - PVR $\geq$ 400 dynes.sec.cm^{-5} (5 Wood units)
    - mPAP $\geq$ 25 mmHg
    - PCWP or LVEDP $\leq$ 15 mmHg
    - Subjects who otherwise meet all the inclusion criteria and none of the exclusion criteria but have not undergone a RHC within the previous 5 years may be considered eligible for the study if they undergo a RHC and then meet the pulmonary hemodynamics criterion
6. 6MWD $\geq$ 100 meters and $\leq$ 450 meters prior to randomization
7. WHO Functional Class II-IV. Subjects with WHO Functional Class IV **should** be treated with prostacyclin or a prostacyclin analog (subcutaneous or intravenous), plus at least one additional PAH specific therapy (ERA or PDE-5), if available to the subject and reimbursed by health insurance
8. Age between 18 and 85 years (inclusive)
9. Willingness to use INOpulse delivery device for at least 12 hours per day
10. Willingness to continue on study drug until subject completes Week 18 assessments
11. Female subjects of childbearing potential must have a negative pre-treatment pregnancy test (serum or urine). All female subjects should take adequate precaution to avoid pregnancy.

Exclusion criteria:

1. Subjects with known HIV infection who have a history within the past 3 months of any opportunistic pulmonary disease (e.g., tuberculosis, Pneumocystis carinii pneumonia, or other pneumonias) at the time of Screening

2. PAH associated with untreated thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders or splenectomy
3. Subjects with pulmonary conditions that may contribute to PAH including, but not limited to, chronic bronchiectasis, cystic fibrosis, or other pulmonary condition that the Investigator may deem to contribute to the severity of the disease or impair the delivery of iNO due to airway disease
4. Subjects receiving riociguat
5. Subjects receiving oral prostanoids as monotherapy
6. PAH associated with significant venous or capillary involvement, known or suspected pulmonary veno-occlusive disease, or pulmonary capillary hemangiomatosis
7. Any subject with WHO PH Groups 2, 3, 4 or 5
8. Subjects with any of the following cardiac abnormalities:
    a. Underlying cardiomyopathy or clinically significant aortic or mitral valve disease in the opinion of the investigator
    b. Left ventricular systolic dysfunction (LVSD), i.e., left ventricular ejection fraction (LVEF) < 40% or left ventricular shortening fraction (LVSF) < 22%, as determined by local reading
    c. Current symptomatic coronary artery disease, myocardial infarction within 1 year, or any coronary artery interventions within 6 months
9. Systemic hypertension defined as systolic blood pressure (SBP) > 160 mmHg and/or diastolic blood pressure (DBP) > 100 mmHg persistent at Screening after a period of rest (treated or untreated)
10. Subjects with a history of deep vein thrombosis, pulmonary embolism/infarction or prothrombotic disorder must have had chronic thromboembolic pulmonary hypertension (CTEPH) excluded by ventilation/perfusion lung (V/Q) scan
11. Severe obstructive lung disease defined as both a forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) < 70% **and** FEV_1 < 55%of predicted value
12. Moderate to severe restrictive lung disease: total lung capacity (TLC) < 60% of predicted; if TLC 60% to 70% predicted, a high resolution CT scan showing diffuse disease or more than mild patchy disease
13. Any subject who develops or has developed a PCWP > 20 mmHg during acute vasodilator testing (AVT)
14. Systemic hypotension defined as SBP < 90 mmHg persistent at Screening after a period of rest
15. Moderate to severe hepatic impairment, i.e., Child-Pugh Class B or C
16. On dialysis
17. Acute or chronic physical impairment (other than dyspnea due to PAH) that would limit the ability to comply with study procedures or adherence to therapy (i.e., 6MWT), including carrying and wearing the pulsed delivery device per study protocol, or medical problem(s) likely to preclude completion of the study
18. Pregnant or breastfeeding females at Screening

19. Administered L-arginine within 1 month prior to Screening
20. Known concomitant life-threatening disease with a life expectancy less than 1 year
21. Atrial septostomy within 3 months preceding randomization
22. The concurrent use of the INOpulse device with a continuous positive airway pressure (CPAP), Bilevel positive airway pressure BiPAP, or any other positive pressure device.
23. Use of investigational drugs or devices within 1 month prior to Screening (other than acute vasodilator testing with iNO)
24. Any underlying medical or psychiatric condition that, in the opinion of the Investigator, makes the subject an unsuitable candidate for the study
25. Any subject who has been enrolled in any previous clinical study with inhaled NO administered through pulse delivery.

Additional Criteria to Continue to Treatment Phase from Run-in period (Week 0 to Week 2)

1. Subjects must demonstrate an average daily usage of the INOpulse device of ≥ 12 hours (rounded to the nearest hour), with no more than 2 days of usage < 8 hours per day, during the initial 2 weeks of study.
2. If a subject experiences clinical worsening during the Screening or Run-in period, the subject will not be eligible to enter into the treatment phase of the study.
3. Subjects who have been randomized at baseline and found not to meet all Inclusion criteria and/or who meet Exclusion criteria during the Run-in period will be withdrawn from the study. These subjects will be replaced to meet total target enrollment.

Part 2 Open Label Period: Diagnosis and main criteria for inclusion and exclusion:

Inclusion Criteria Part 2:

1. Informed Consent Form prior to the initiation of any study mandated procedures or assessments
2. Subject must have completed 18 weeks of blinded therapy and all assessments at week 18
3. In the opinion of the Investigator, open label treatment is in the best interest of the subject after 18 weeks of blinded treatment is completed

Exclusion Criteria Part 2 Open Label Period:

1. Subject has initiated therapy with Riociguat

Investigational product, dosage and mode of administration:

Part 1 Blinded Treatment Period:

In a randomized, double-blind manner, all subjects randomized to iNO at a dose setting of 75 mcg/kg IBW/hr will be treated by means of an INOpulse delivery device and product-specific cannula. The active study drug, nitric oxide for inhalation (iNO), will be provided in size 0.074 liter aluminum cartridge at a concentration of 6.0 mg/L (4880 ppm). All subjects will change cartridges approximately every 12 hours.

All subjects randomized to receive iNO will receive 15 mcg/kg IBW/hr for the first 2 weeks (Run-in phase) followed by iNO at 75 mcg/kg IBW/hr for 16 weeks.

Part 2 Open Label Period: All subjects enrolled in Part 2 Open label treatment will receive iNO at 75 mcg/kg IBW/hr.
Duration of treatment: **Part 1 Blinded Treatment Period:** Until the subject has completed 18 weeks of blinded treatment **Part 2 Open Label Period**: Subjects will remain on therapy until the investigational drug device is approved and available as a marketed product or the Sponsor decides to discontinue development of iNO for PAH or the Sponsor decides to terminate the study.
Reference therapy, dosage and mode of administration: **Part 1 Blinded Treatment Period:** In a randomized, double-blind manner, all subjects randomized to placebo at a dose setting of 75 mcg/kg IBW/hr will be treated by means of an INOpulse delivery device and product-specific cannula. Placebo to match study drug and supplied in size 0.074 liter aluminum cartridge containing N_2, 99.999% gas. All subjects will change cartridges approximately every 12 hours. All subjects randomized to receive placebo will receive 15 mcg/kg IBW/hr for the first 2 weeks (Run-in phase) followed by placebo at a dose setting of 75 mcg/kg IBW/hr for 16 weeks. **Part 2 Open Label Phase:** Subjects will receive open label treatment only 75 mcg/kg IBW/hr, there is no placebo.

Statistical methods:

An intent-to-treat (ITT) population that consists of all randomized subjects who remained eligible after the Run-in period will be used for all the efficacy analyses, each patient will be analyzed according to the treatment to which they were randomized.

A safety population that includes all randomized subjects who receive the study treatment and who remained eligible after the Run-in period will be used for all the safety analyses. In addition, an analysis of safety for all randomized subjects who receive the study treatment and who became ineligible after the Run-in period will be conducted. For the safety population, each patient will be analyzed according to the treatment administered.

The primary statistical test for the primary endpoint will be performed using a repeated measures mixed model with the baseline stratification factor (i.e., the prostanoid usage status) treatment arm, week and treatment-by-week as the fixed effects. As a covariate, baseline 6MWD assessment (defined by the average of two 6MWTs at Week 2 after the completion of the run-in phase) will be included in the model. In case the normality assumption is invalid, the primary efficacy endpoint will be analyzed using the van Elteren test stratified by the prostanoid usage status. Summary statistics will be provided for all study variables with descriptive statistics (number of observations, mean, standard deviation, median, minimum, maximum and from the analysis model the least squares means, SAE's and confidence limits) for numerical (or continuous) variables and with frequency and percentage for categorical variables.

Exploratory analyses will be performed to evaluate the effects of demographics and baseline characteristics on the efficacy response with appropriate statistical methods. Subgroup analyses based on study drug usage, background therapies, demographics and baseline characteristics, as well as other study compliance status will be conducted. Additional statistical methods such as mixed effects model and Cochran-Mantel-Haenszel (CMH) test (for dichotomized response analysis) may be utilized in the exploratory analyses.

Interim analyses will be conducted when data is available from 75 patients. The purpose of the interim analysis is to stop the trial early for efficacy or futility or to continue the trial to 150 or 188 patients (total randomized is higher to account for an anticipated 20% drop out rate). Group sequential early stopping criteria and sample size re-estimation methodology are further described in the statistics section of this protocol. They are constructed to control overall type 1 error at 0.025, 1-sided. Simulations assuming true underlying mean treatment difference in 6MWD ranging from 30-70 meters and SD's from 50 to 75 meters yielded >87% power for all cases except the most extreme case (mean difference 30 meters and SD 75, for which power was ~71%.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
6MWD	6 minute walk distance
6MWT	6 minute walk test
AE	adverse event
AESI	adverse event of special interest
ANOVA	analysis of variance
APAH	associated pulmonary arterial hypertension
AVT	acute vasodilator testing
BDS	Borg dyspnea score
BiPAP	Bilevel positive airway pressure
BNP	B-type natriuretic peptide
BP	blood pressure
Bpm	beats per minute
BSA	body surface area
CDC	Central Distribution Center
CI	cardiac index
CO	cardiac output
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CRO	clinical research organization
CTD	connective tissue disease
CTEPH	chronic thromboembolic pulmonary hypertension
DLCO	diffusing capacity for the lungs measured using carbon monoxide
DMC	Data Monitoring Committee

Abbreviation or Specialist Term	Explanation
DBP	diastolic blood pressure
dPAP	diastolic pulmonary artery pressure
EAS	electronic adjudication system
eCRF	electronic case report form
ECG	electrocardiogram
ERA	endothelin receptor antagonists
EOS	end of study
FEV_1	forced expiratory volume in 1 second
FiO_2	fraction of inspired oxygen
FPFV	First Patient First Visit
FVC	forced vital capacity
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HR	heart rate
HRQoL	health related quality of life
HRU	healthcare resource utilization
IA	Interim Analysis
IBW	ideal body weight
IEC	Independent Ethics Committee
ICEC	Independent Clinical Events Committee
ICF	informed consent form
ICH	International Conference of Harmonization
iNO	inhaled nitric oxide
IPAH	idiopathic pulmonary arterial hypertension
IRB	Institutional Review Board

Abbreviation or Specialist Term	Explanation
ITT	intent-to-treat
IRT	Interactive Response Technology
LPFV	Last Patient First Visit
LPLV	Last Patient Last Visit
LTOT	long term oxygen therapy
LVEDP	left ventricular end diastolic pressure
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
LVSF	left ventricular shortening fraction
M	mean
MedDRA	Medical Dictionary for Regulatory Activities
MetHgb	methemoglobin
ml	milliliter
N_2	nitrogen
NO	nitric oxide
NT-proBNP	N-terminal of the prohormone brain natriuretic peptide
O_2	oxygen
PAH	pulmonary arterial hypertension
PAP	pulmonary arterial pressure
PCWP	pulmonary capillary wedge pressure
PDE-5	phosphodiesterase type-5
PH	pulmonary hypertension
ppm	parts per million
PVR	pulmonary vascular resistance
RAP	right atrial pressure

Abbreviation or Specialist Term	Explanation
RHC	right heart catheterization
RR	respiratory rate
SAE	serious adverse event
SpO_2	oxygen saturation by pulse oximeter
SAP	systemic artery pressure
SAR	serious adverse reaction
SBP	systolic blood pressure
SC	Steering Committee
S/D	Systolic/diastolic
SD	Standard Deviation
SMQ	standardized MedDRA queries
sPAP	systolic pulmonary artery pressure
SVR	systemic vascular resistance
TLC	total lung capacity
TPR	total pulmonary resistance
TTCW	time to clinical worsening
WHO	World Health Organization

5. INTRODUCTION

This is a Phase 3, placebo controlled, double-blind, randomized, clinical study to determine safety, tolerability and efficacy of pulsed inhaled nitric oxide (iNO) versus placebo as add-on therapy in subjects with pulmonary arterial hypertension (PAH) who remain symptomatic on approved PAH monotherapy or combination approved PAH therapy and long term oxygen therapy (LTOT)(Part 1 and Part 2).

Pulmonary arterial hypertension is a progressive disease characterized by progressive pulmonary vascular arteriopathy leading to elevation in pulmonary vascular resistance (PVR) and pulmonary arterial pressure (PAP) with right ventricular failure and death if untreated (McLaughlin 2009; Barst 2009; McGoon 2009; Badesch 2007). Additionally, many subjects die on monotherapy or combination approved PAH therapy. The overall current 5-year survival with current standard of care is only 60% (Benza 2010). The pathogenesis of PAH remains unclear, but an imbalance between vascular cell proliferation and apoptosis, an influx of cellular inflammation, excess vasoconstriction, and in situ thrombosis all appear to contribute to the narrowing or obliteration of the pulmonary arteriolar lumens resulting in increased PVR (McLaughlin 2009). Deficiencies in the vasodilator/anti-proliferative agents prostacyclin and nitric oxide have also been observed as well as increased production of the vasoconstrictor/proliferative agents endothelin-1 and thromboxane.

There is no cure for PAH and the 5-year survival rate for idiopathic or heritable PAH was approximately 30% prior to the availability of targeted PAH therapies based on Registry data from the 1980s (Anderson 2010). However, in recent years, effective therapies targeting specific endothelial abnormalities have emerged. Currently approved treatments have been demonstrated to have both short- and long-term efficacy. These include: synthetic prostacyclin, i.e., epoprostenol, a prostacyclin analog, treprostinil or iloprost; an endothelin receptor antagonist (ERA), i.e., bosentan, ambrisentan, or macitentan; phosphodiesterase type-5 (PDE-5) inhibitors, i.e., sildenafil and tadalafil; and soluble guanylate cyclase (sGC) stimulators, i.e., riociguat (McLaughlin 2006; Barst 2009; McGoon 2009; Badesch 2007; Anderson 2010; Ghofrani 2013). These medications may improve symptoms, exercise capacity, and clinical outcome, but may be limited by either parenteral delivery system, the need for frequent laboratory monitoring, frequent dosing schedules, or unwanted side effects. Because of the availability of several agents working via different mechanisms, interest has developed in add on (i.e., combination) therapy. This strategy has proven successful in improving clinical outcomes in some subjects. Yet, as stated above, despite these significant advances in the treatment of PAH, the current 5-year survival for Group 1 PAH is ~60% utilizing the available approved PAH therapies (Anderson 2010). Patients who are receiving prostacyclin therapy, ERA, and PDE-5, have no further treatment options other than atrial septostomy and lung transplantation.

PAH is associated with impaired release of nitric oxide at least in part because of reduced expression of nitric oxide synthase in the vascular endothelium of pulmonary arteries (McLaughlin 2009; Barst 2009; McGoon 2009; Badesch 2007; Anderson 2010). Thus, chronic administration of iNO may be viewed as replacement therapy in some subjects with PAH making it a logical choice for clinical evaluation.

5.1. Pulsed Inhaled Nitric Oxide for Treatment of Long-Term Pulmonary Arterial Hypertension

The effects of long-term administration of iNO to patients with PAH, chronic obstructive pulmonary disease (COPD), and idiopathic pulmonary fibrosis (IPF) have been published. Approximately 100 patients received iNO acutely, approximately 40 of whom continued to receive long-term iNO for up to 2 years (Ashutosh 2000, Channick 1996, Germann 1998, Perez-Penate 2005, Perez-Penate 2008, Vonbank 2003, Yung 2001). Overall, review of the published medical literature and clinical experience indicates that iNO at doses of 0.013 to 0.1 mg/kg per hour for up to 2 years appears safe and suggests efficacy for the treatment of pulmonary hypertension (PH), including Pulmonary Hypertension Group 1.

Inhaled NO offers an additional treatment option for patients, in particular patients who are already receiving prostacyclin therapy, ERA, and PDE-5, who have no other medical treatment options. Inhaled NO has the advantage of being able to be added to all other available PAH therapies with the exception of riociguat. The riociguat label excludes addition of NO donors because of the side effects of systemic hypotension.

Bellerophon Pulse Technologies recently completed Part 1 of a Phase 2 clinical trial of iNO/INOpulse for PAH in the United States and Canada (Study IK-7001-PAH-201). The key inclusion criteria for subjects in this trial were: pulmonary hypertension WHO Group I, on at least one other PAH medication for at least 12 weeks prior to treatment with iNO/INOpulse, and demonstrated ability to walk between 100 and 450 meters within 6 minutes. The Part 1 placebo-controlled, double-blind clinical trial randomized 80 subjects in a 1:1:1 fashion to placebo or to one of two active iNO doses—25 or 75 mcg/kg IBW/hr for 16 weeks. Subjects who completed Part 1 of the trial were able to enroll in an open-label, long-term extension portion of the study (Part 2), in which all subjects received one of two doses iNO. The objective in Part 2 was to explore the long-term safety and tolerability of therapy.

The primary endpoint of Part 1 was change in pulmonary vascular resistance (PVR) from baseline at 16 weeks, and the main secondary endpoint was change in placebo-adjusted 6-minute walk distance (6MWD) over the same period. The baseline characteristics seemed to indicate that subjects in the iNO groups had more severe disease. LTOT use at baseline was 78% and 59% in the 75 and 25 mcg/kg IBW/hr cohorts, respectively, compared to 46% in the placebo cohort. Baseline PVR values were higher in the higher dose group, and 6MWDs were lower in the same group. The results in the ITT population showed a trend toward a lowering of PVR with iNO treatment and an increase in 6MWD, but this did not reach statistical significance.

Adherence to therapy was widely variable. LTOT use was recorded at baseline, and subjects using LTOT at baseline were more adherent to using the investigational INOpulse delivery device (hereafter INOpulse device), defined retrospectively as an average use of ≥ 12 hours per day—specifically, subjects using LTOT had a rate of 71% adherence as compared with 32% adherence in those subjects not using LTOT. Based on this finding, we conducted post hoc, exploratory analyses of LTOT combined with iNO for ≥ 12 hours a day.

In the post-hoc, unplanned analyses, the subgroup of subjects who used the INOpulse device for an average ≥ 12 hours per day with LTOT (n = 35), showed a positive trend towards a decrease in PVR with 25 and 75 mcg/kg IBW/hr. There was a clinically meaningful improvement in 6MWD in comparing the 75 mcg/kg IBW/hr dose group with the placebo group (52 ± 42 [mean ± SD] vs. -17 ± 32 [mean ± SD]). There was on average a non-significant increase in 6MWD of 26 meters in subjects treated with 25 mcg/kg IBW/hr. Improvements in 6MWD were the same for subjects treated with oral PAH therapies alone, and subjects with prostacyclin therapy plus therapy with either a PDE-5 or ERA. The results were similar to those subjects with inhaled iloprost where there was no significant change in PVR prior to inhalation of iloprost at EOS versus baseline, but a significant improvement in 6MWD (Olschewski 2002).

Inhaled NO was relatively well-tolerated in Part 1 of the trial. The SAEs were balanced between all 3 cohorts (reference Investigator Brochure for additional detail).

Eighty-one percent of subjects elected to enter into the long-term extension trial.

The results of Part 2 of the study demonstrated that pulsed iNO was well tolerated beyond the initial 16-week treatment period in Part 1. The incidence of Respiratory AEs and related Respiratory AEs in the Part 2 of the study were comparable in both the iNO 75 and iNO 25 treatment groups. No subjects had a MetHb level ≥7%.

Subjects with LTOT are more likely to be compliant and may have better outcomes. In the Phase 3 trial, recruitment will be limited to only subjects on LTOT.

5.2. Inhaled Nitric Oxide

Inhaled nitric oxide, a prescription pharmaceutical drug under the brand name of INOmax® (nitric oxide) for inhalation, is available commercially as a gaseous mixture of NO and nitrogen (N_2). INOmax is approved and marketed by Ikaria Inc. (now owned by Mallinckrodt Pharmaceuticals) and The Linde Group in the US (December 1999), European Union (August 2001) and other national authorities, for neonates (> 34 weeks old) with hypoxic respiratory failure associated with clinical or echocardiographic evidence of PH when used in conjunction with ventilatory support and other appropriate agents.

Nitric oxide is a selective pulmonary vasodilator. The mechanism of NO-mediated vasodilation occurs via the activation of soluble guanylate cyclase, the production of cyclic guanosine monophosphate (cGMP), and subsequent relaxation of vascular smooth muscle. Inhaled NO produces pulmonary vasodilation and clearly does not affect systemic vascular beds by virtue of its high affinity for hemoglobin and rapid inactivation. In a number of animal species and under several vasoconstrictive stimuli, iNO produced rapid and effective pulmonary vasodilation at concentrations between 5 and 80 parts per million (ppm). Evaluations in the newborn lamb demonstrated that iNO selectively reverses hypoxic pulmonary vasoconstriction, with maximal pulmonary vasodilation produced by NO concentrations of 80 ppm. In an animal model of persistent PH of the newborn (PPHN), neonatal lambs displayed a marked and rapid pulmonary vasodilation that improved oxygenation at inhaled NO concentrations of 100 ppm.

5.3. INOpulse Device

For the indication of PAH, iNO is being developed as a drug/device combination therapy to be used with the INOpulse delivery device.

The INOpulse device is a complete, integrated system that uses a 0.074 liter aluminum cartridge containing a concentration of 6.0 mg/L (4880 ppm) of NO gas. The device is lightweight, portable, allowing NO to be administered via a nasal cannula to spontaneously breathing subjects. These features make it ideal for use in an ambulatory setting. The main advantage of the INOpulse device for spontaneously breathing subjects lies in its ability to deliver precise, preset NO doses over time, independent of the subject's respiration rate and tidal volume. Prescribed doses of iNO are delivered through the INOpulse according to amount of drug per ideal body weight (IBW) per hour (i.e., mcg/kg IBW/hr). The iNO dose is pulsed over the first half of the subject's inspiration rather than inhaled throughout the entire inspiratory period and the hourly set dose is accurately delivered throughout the hour.

6. OBJECTIVES

Part 1 Blinded Treatment Period

6.1. Primary Objective

The primary objective in this study is to evaluate the efficacy of iNO on exercise using 6-minute walk distance (6MWD) in subjects with PAH currently receiving background PAH medication and LTOT.

6.1.1. Secondary Objectives

The secondary objectives in this study are:

1. To evaluate the time to clinical worsening (TTCW)
2. To evaluate change in World Health Organization (WHO) Functional Class

6.1.2. Safety Objectives

The safety objectives in this study are to evaluate the safety and tolerability of iNO.

6.1.3. Tertiary Objectives

The tertiary objectives in this study are:

1. To evaluate changes in health-related quality of life using the Short Form-36 (SF-36) version 2 health survey
2. To evaluate the impact of iNO on pulmonary hemodynamics in a subset of subjects
3. To evaluate the changes in right ventricular (RV) and left ventricular (LV) function as measured by echocardiography, in a subset of subjects
4. To evaluate change in N-terminal of the prohormone brain natriuretic peptide (NT-proBNP)
5. To evaluate change in Borg dyspnea score immediately following 6-minute walk test (6MWT)
6. To evaluate change in 6MWD as related to degree of correlation between drug adherence and clinical efficacy measurement
7. To evaluate subjects with unsatisfactory clinical response
8. To evaluate the impact of iNO on frequency of heart-lung or lung transplantation, and deaths while awaiting transplantation
9. To evaluate the impact of iNO on medical resource utilization

6.2. Part 2 -Open Label Period:

6.2.1. Primary Objective:

1. To Evaluate the long term safety and tolerability of iNO

6.2.2. Secondary Objective:

1. To evaluate the change in exercise tolerance in subjects who switch from placebo to active therapy

7. ENDPOINTS

7.1. Part 1 Blinded Treatment Period

7.1.1. Primary Endpoint

The primary endpoint in this study is to assess the efficacy of iNO as measured by the placebo-adjusted change in 6MWD from baseline to 18 weeks.

7.1.2. Secondary Endpoints

The secondary endpoints include:

1. TTCW, the time (in days) from start of treatment to first event (first day the event is noted), with iNO as compared to placebo, measured from baseline to 18 weeks . TTCW event is defined as any of the following:
    a. Death (all-cause mortality)
    b. Atrial septostomy
    c. Hospitalization due to worsening of PAH (adjudicated)
    d. Start of new specific PAH treatment (endothelin receptor antagonists [ERAs], phosphodiesterase type-5 [PDE-5] inhibitors or prostanoids), an increase in the dose of an ERA or PDE-5, increase in the dose or frequency of an inhaled prostanoids, or an increase in the dose of an intravenous or subcutaneous prostanoids by >10%.
    e. Decrease of >15% from baseline or >30% compared with the last study related measurement in 6MWD should be confirmed by a repeat measurement performed at least 14 days later
    f. Worsening of WHO Functional Class (e.g., from Class II to Class III or IV, OR Class III to Class IV); and should be confirmed by a repeat assessment at least 14 days later
2. Change in WHO Functional Class, with iNO as compared to placebo, from baseline to 18 weeks

7.1.3. Tertiary Endpoints

The tertiary endpoints in this study include:

1. Change in health-related quality of life (using SF-36 version 2 health survey), with iNO as compared to placebo, from baseline to 18 weeks
2. Change in pulmonary hemodynamics (i.e., cardiac output [CO], cardiac index [CI], mean pulmonary artery pressure [mPAP], mean pulmonary capillary wedge pressure [mPCWP], systolic pulmonary artery pressure [sPAP], diastolic pulmonary artery pressure [dPAP], pulmonary vascular resistance [PVR], oxygen saturation by pulse oximeter [SpO_2], mixed venous O_2, and right atrial pressure [RAP]), measured by right heart catheterization (RHC), with iNO as compared to placebo, from baseline to 18 weeks, in a subset of subjects (approximately 50), at selected sites
3. Change in echocardiogram measurements right ventricular function (including right ventricular fractional area change, systolic pulmonary artery pressure [sPAP], tricuspid

annular motion/tricuspid annular plane systolic excursion, tricuspid annular systolic velocity, and Tei index) and left ventricular function (including left ventricular ejection fraction [LVEF], LV size, and improvement in LV early diastolic relaxation velocity), with iNO as compared to placebo, from baseline to 18 weeks, in a subset of subjects (approximately 50), at selected sites

4. Change in NT-proBNP, with iNO as compared to placebo, from screening to 18 weeks
5. Change in Borg dyspnea score immediately following 6MWT, with iNO as compared to placebo, from baseline to 18 weeks
6. Change in 6MWD as related to degree of drug adherence, with iNO as compared to placebo, from baseline to 18 weeks
7. The number of subjects with unsatisfactory clinical response, with iNO as compared to placebo, from baseline to 18 weeks. Defined as: WHO Functional Class III or IV symptoms with no improvement in 6MWD
8. Number of subjects undergoing heart-lung or lung transplantation, number of subjects listed for transplantation, and deaths while awaiting transplantation, from baseline to 18 weeks
9. Medical resource utilization, with iNO as compared to placebo, from baseline to 18 weeks

7.1.4. Safety Endpoints

The safety endpoints include:

1. Incidence and severity of adverse events (AEs)
2. Incidence of device malfunction and/or device failure leading to an AE
3. Incidence of rebound pulmonary hypertension (PH)
4. Clinically significant changes in:
   a. Clinical laboratory tests
   b. Pulmonary function tests
   c. Vital signs

7.2. Part 2 Open Label Period:

7.2.1 Primary Endpoint:

1. The incidence of AEs and SAEs with long term therapy

7.2.2 Secondary Endpoint:

1. To evaluate the change in 6MWD in subjects who switch from placebo to active therapy at 4 months, 8 months and 12 months of therapy

8. STUDY DESIGN

8.1. Overall Study Design

This is a multi-center, randomized, double-blind, placebo-controlled, parallel-group design to determine the efficacy, safety and tolerability of pulsed iNO versus placebo in symptomatic subjects with PAH currently receiving background PAH medication and LTOT.

All subjects will be treated by means of a blinded INOpulse delivery device. The device measures daily exposure (minutes per day in use, measured as breath detection).

The study consists of two parts Part 1, the Blinded Treatment Period, and Part 2, the Open Label Extension Period. After the Screening period, the subjects will be randomized at Week 0 then enter a double-blind, Run-in period (Week 0 to Week 2) to assess their eligibility to continue in the study by their usage of the INOpulse device for an average ≥ 12 hours (rounded to the nearest hour) per day with no more than 2 days of usage < 8 hours per day. All subjects will be analyzed for safety during this Run-in period. Those subjects not meeting the 12 hour INOpulse device usage requirement (by Week 2) will be discontinued and ineligible to proceed to the next phase of treatment. Subjects meeting the device usage requirement, and all Inclusion/Exclusion criterion (by Week 2), will qualify to enter into the next phase of treatment.

Subjects who are unable to meet enrollment criteria during the Run-in period may be rescreened at the discretion of the Sponsor.

Subjects will be randomized to a treatment assignment as described in Table 1 below. Subjects randomized to active iNO will receive a reduced dose of iNO during run in and subjects randomized to placebo will receive placebo during run in.

At Baseline, all subjects will be stratified for prostanoids usage.

LTOT flow rates should be kept constant throughout the study unless the subject has persistent desaturations to less than 88% of SpO_2, or otherwise clinically indicated. LTOT flow rate with the estimated length of use per day must be documented in the eCRF at all visits. Subjects will be encouraged to use their oxygen during the day and night as prescribed by their treating physician. All 6MWTs will be performed while subjects are receiving oxygen and carrying the INOpulse device (including baseline assessments).

Additional specific PAH therapies may be added only for evidence of clinical worsening due to PAH as defined in the protocol throughout the trial.

Subjects will remain in the study and continue to receive blinded treatment according to their randomization for an additional 16 weeks for a total of 18 weeks.

Part 2-Open Label Period -Subjects will be offered open label therapy when a subject completes 18 weeks of blinded drug therapy.

Subjects will be given the opportunity continue in Part 2 Open Label Treatment and will receive iNO at 75 mcg/kg IBW/hr with the INOpulse delivery device until the drug-device investigational product is approved and available as a marketed product or the Sponsor decides to discontinue development of iNO for PAH.

8.2. Treatment Assignment

Subjects who meet all enrollment criteria during the Screening period will be randomized in a 1:1 ratio into one of two dosing cohorts as presented in Table 1. Ninety-four subjects will be enrolled in each cohort.

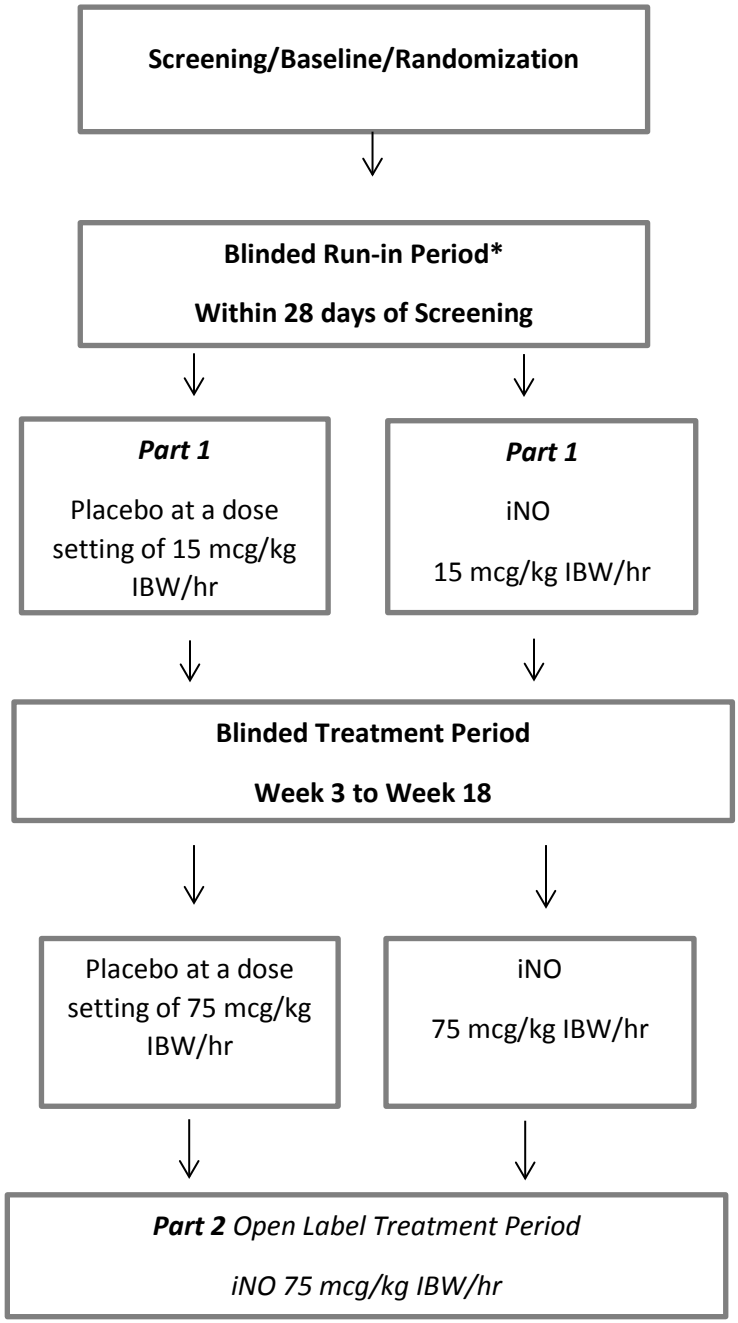
Table 1: Dosing Assignments for Run-in and Treatment Periods

	Part 1 Blinded Treatment Period		**Part 2 Open Label Period**
Cohort	**Run-in Period Week 0 to Week 2**	**Treatment Period Week 3 to Week 18**	**Open Label Treatment**
Cohort 1: Placebo	Placebo at a dose setting of 15 mcg/kg IBW/hr	Placebo at a dose setting of 75 mcg/kg IBW/hr	iNO 75 mcg/kg IBW/hr
Cohort 2: iNO 75 mcg/kg IBW/hr	iNO 15 mcg/kg IBW/hr	iNO 75 mcg/kg IBW/hr	iNO 75 mcg/kg IBW/hr

Note: Study drug is dosed according to IBW and not actual body weight. IBW is determined by a subject's gender and height, and therefore will not change during the study period.

A study flow diagram is presented in Figure 1.

Figure 1: Study Design



*All subjects during the Run-in period must be willing to comply with usage of INOpulse device for ≥ 12 hours (rounded to the nearest hour) per day, with no more than 2 days of usage < 8 hours per day. Subjects randomized to iNO will receive 15 mcg/kg IBW/hr for the first 2 weeks (Run-in phase) followed by iNO at 75 mcg/kg IBW/hr dose for the Treatment Period. Subjects randomized to Placebo will receive Placebo product 15 mcg/kg IBW/hr at a delivery setting matching the treatment groups.

8.3. Study Design Rationale

The proposed study design allows for determination of whether iNO at a dose of 75 mcg/kg IBW/hr delivered via the INOpulse delivery device for up to 24 hours per day demonstrates efficacy of iNO in subjects with PAH concomitantly using approved PAH specific medication and LTOT. The primary endpoint will be change in 6MWD at 18 weeks, but a key secondary endpoint will be TTCW. Subjects, Investigators, and Sponsor will remain blinded to treatment until the last subject's completion of treatment at 18 weeks.

To ensure compliance with device usage, a double-blind, Run-in period (Week 0 to Week 2) will assess subject eligibility to continue in the study by their usage of the INOpulse device for an average ≥ 12 hours (as described in Section 8.1). Subjects will be randomized to placebo or iNO at 15 mcg/kg IBW/hr. The 15 mcg/kg IBW/hr dose is considered an ineffective dose. Use of low dose NO during the Run-in period is intended to avoid potential unblinding when the subject enters the treatment phase due to potential difference in smell.

9. STUDY POPULATION

9.1. Population

In accordance with inclusion criteria, the study population will consist of subjects 18 to 85 years of age with a confirmed diagnosis of PAH, confirmed by RHC within the previous 5 years.

9.2. Number of Subjects to be Studied

A total of 188 subjects (94 per dosing cohort) will be randomized to achieve 150 completed subjects. Total randomized will be higher to account for an anticipated 20% drop out rate.

9.3. Inclusion Criteria

Part 1 Blinded Treatment Period

Subjects must meet all of the following inclusion criteria to be enrolled and eligible to participate in the study.

1. Signed Informed Consent Form prior to the initiation of any study mandated procedures or assessments
2. A confirmed diagnosis of PAH Group 1 who have either idiopathic PAH (IPAH), heritable PAH, drug and toxin-induced PAH, associated PAH (APAH) with connective tissue disease (CTD), APAH with congenital heart disease (unrepaired or repaired at least 1 year prior to Screening), APAH with human immunodeficiency virus (HIV), or APAH with portal hypertension
3. Subjects receiving at least one PAH specific therapy (ERA or PDE-5 inhibitor, or inhaled, subcutaneous, or intravenous prostacyclin or a prostacyclin analog) with the same type of therapy for at least 3 months with stable dosing 4 weeks prior to Screening. (Subjects should be receiving optimal therapy according to the disease severity)
4. Subjects using oxygen therapy by nasal cannula for at least 4 weeks prior to Screening
5. PAH diagnosis confirmed by RHC within the previous 5 years, according to the following definitions:
    - PVR $\geq$ 400 dynes.sec.cm^{-5} (5 Wood units)
    - mPAP $\geq$ 25 mmHg
    - PCWP or LVEDP $\leq$ 15 mmHg
    - Subjects who otherwise meet all the inclusion criteria and none of the exclusion criteria but have not undergone a RHC within the previous 5 years may be considered eligible for the study if they undergo a RHC and then meet the pulmonary hemodynamics criterion
6. 6MWD $\geq$ 100 meters and $\leq$ 450 meters prior to randomization
7. WHO Functional Class II-IV. Subjects with WHO Functional Class IV **should** be treated with prostacyclin or a prostacyclin analog (subcutaneous or intravenous), plus at least one

additional PAH specific therapy (ERA or PDE-5), if available to the subject and reimbursed by health insurance

8. Age between 18 and 85 years (inclusive)
9. Willingness to use INOpulse delivery device for at least 12 hours per day
10. Willingness to continue on study drug until the subject has completed Week 18 assessments (EOS)
11. Female subjects of childbearing potential must have a negative pre-treatment pregnancy test (serum or urine). All female subjects should take adequate precaution to avoid pregnancy.

9.4. Exclusion Criteria

Exclusion criterion in this study includes the following:

1. Subjects with known HIV infection who have a history within the past 3 months of any opportunistic pulmonary disease (e.g., tuberculosis, *Pneumocystis carinii* pneumonia, or other pneumonias) at the time of Screening
2. PAH associated with, untreated thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders or splenectomy
3. Subjects with pulmonary conditions that may contribute to PAH including, but not limited to, chronic bronchiectasis, cystic fibrosis, or other pulmonary condition that the Investigator may deem to contribute to the severity of the disease or impair the delivery of iNO due to airway disease
4. Subjects receiving riociguat
5. Subjects receiving oral prostanoids as monotherapy
6. PAH associated with significant venous or capillary involvement, known or suspected pulmonary veno-occlusive disease, or pulmonary capillary hemangiomatosis
7. Any subject with WHO PH Groups 2, 3, 4 or 5
8. Subjects with any of the following cardiac abnormalities:
    a. Underlying cardiomyopathy or clinically significant aortic or mitral valve disease in the opinion of the investigator
    b. Left ventricular systolic dysfunction (LVSD), i.e., left ventricular ejection fraction (LVEF) < 40% or left ventricular shortening fraction (LVSF) < 22%, as determined by local reading
    c. Current symptomatic coronary artery disease, myocardial infarction within 1 year, or any coronary artery interventions within 6 months
9. Systemic hypertension defined as systolic blood pressure (SBP) > 160 mmHg and/or diastolic blood pressure (DBP) > 100 mmHg persistent at Screening after a period of rest (treated or untreated)

10. Subjects with a history of deep vein thrombosis, pulmonary embolism/infarction or prothrombotic disorder must have had chronic thromboembolic pulmonary hypertension (CTEPH) excluded by ventilation/perfusion lung (V/Q) scan
11. Severe obstructive lung disease defined as both a forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) < 70% **and** FEV_1 < 55% of predicted value
12. Moderate to severe restrictive lung disease: total lung capacity (TLC) < 60% of predicted; if TLC 60% to 70% predicted, a high resolution CT scan showing diffuse disease or more than mild patchy disease
13. Any subject who develops or has developed a PCWP > 20 mmHg during acute vasodilator testing (AVT)
14. Systemic hypotension defined as SBP < 90 mmHg persistent at Screening after a period of rest
15. Moderate to severe hepatic impairment, i.e., Child-Pugh Class B or C
16. On dialysis
17. Acute or chronic physical impairment (other than dyspnea due to PAH) that would limit the ability to comply with study procedures or adherence to therapy (i.e., 6MWT), including carrying and wearing the pulsed delivery device per study protocol, or medical problem(s) likely to preclude completion of the study
18. Pregnant or breastfeeding females at Screening
19. Administered L-arginine within 1 month prior to Screening
20. Known concomitant life-threatening disease with a life expectancy less than 1 year
21. Atrial septostomy within 3 months preceding randomization
22. The concurrent use of the INOpulse device with a continuous positive airway pressure (CPAP), Bilevel positive airway presure BiPAP, or any other positive pressure device.
23. Use of investigational drugs or devices within 1 month prior to Screening (other than acute vasodilator testing with iNO)
24. Any underlying medical or psychiatric condition that, in the opinion of the Investigator, makes the subject an unsuitable candidate for the study
25. Any subject who has been enrolled in any previous clinical study with inhaled NO administered through pulse delivery.

Additional Criteria to Continue to Treatment Phase from Run-in period (Week 0 to Week 2)

1. Subjects must demonstrate an average daily usage of the INOpulse device of ≥ 12 hours (rounded to the nearest hour) with no more than 2 days of usage < 8 hours per day, during the initial 2 weeks of study.

2. If a subject experiences clinical worsening during the Screening or Run-in period, the subject will not be eligible to enter into the treatment phase of the study.
3. Subjects who have been randomized at baseline and found not to meet all Inclusion criteria and/or who meet Exclusion criteria during the Run-in period will be withdrawn from the study, these subjects will be replaced to meet total target enrollment.

Part 2 Open Label Period:

Diagnosis and main criteria for inclusion and exclusion:

Inclusion Criteria Part 2:

1. Informed Consent Form prior to the initiation of any study mandated procedures or assessments
2. Subject must have completed 18 weeks of blinded therapy and all assessments at week 18
3. In the opinion of the Investigator open label treatment is in the best interest of the subject after one year of blinded treatment is completed or at the time the last patient is randomized

Exclusion Criteria Part 2 Open Label Period:

1. Subject has initiated therapy with riociguat

10. SUBJECT DISCONTINUATION, WITHDRAWAL AND TERMINATION FROM THE STUDY, SUBJECT REPLACEMENT, AND PROTOCOL DEVIATION CRITERIA

10.1. Subject Discontinuation from Study Drug/Device

Any subject who is discontinued from the study drug will be encouraged to perform all procedures and assessments as appropriate until week 18. Vital status will be determined at the EOS on all subjects who prematurely discontinue. The specific reason for discontinuation will be documented in the eCRF. Subjects may be discontinued due to the following:

1. In the opinion of the Investigator, it is in the subject's best interests to discontinue study drug.
2. Subject no longer wishes to continue using the drug/device.
3. A subject becomes pregnant.
4. In the opinion of the Investigator, the subject experiences clinically significant rebound PH temporally associated with acute withdrawal of study drug.
5. If a subject experiences any of the following: death, atrial septostomy, lung or heart-lung transplantation.

10.2. Subject Withdrawal from Study

Subjects may be considered withdrawn from the study if they meet the following criteria. If the subject does not wish to continue study assessments, **every effort should be made to obtain consent for contact of the subject, or the subject's family member or friends, to establish vital status at EOS.**

- Subjects have the right to withdraw consent at any time and for any reason without prejudice to his/her future medical care by the physician or the institution. The specific reason for subject withdrawal of consent will be documented in the eCRF.

10.2.1. Subject Withdrawal During Run-In Period

1. Subjects who have been randomized during the Run-in period and found not to meet Inclusion criteria and/or meet Exclusion criteria (at Week 2), will be withdrawn from the study. Additional subjects will be enrolled to meet total target enrollment.
2. Subjects who do not demonstrate an average daily usage of the INOpulse device of ≥ 12 hours (rounded to the nearest hour), or who have more than 2 days of usage < 8 hours per day during the initial 2 weeks of study, will be withdrawn. Additional subjects will be enrolled to meet total target enrollment.
3. Subjects who have clinical worsening of PAH during the Run-in period will be withdrawn. Additional subjects will be enrolled to meet total target enrollment.

10.3. Subjects Lost to Follow-Up

Subjects who do not complete their scheduled visits, have not died, and have not officially withdrawn from the study are considered lost to follow-up. Site personnel should make every reasonable effort to locate and communicate with the subject using all available methods (e.g., telephone, email, certified letter, in-person contact) requesting the subject contact the Study Coordinator or Principal Investigator. Attempts to locate subjects must begin immediately after a missed visit; delays in locating the subject increase the chance of the subject becoming lost to follow-up.

Attempts to contact the subject should be documented in the subject's medical records and documented in the eCRF.

The following contact procedure is recommended at each time point:

- A minimum of 2 telephone calls on different days over the specified follow-up windows should be recorded in the source documentation including date, time, and site personnel initials attempting to contact the subject.
- If these attempts are unsuccessful, a certified letter (or similar) should be sent to the subject (or other method of confirming notification that a letter was delivered).
- All efforts should be made to obtain the vital status at EOS, including public information sources.
- An independent vendor may be used to assist in location of lost to follow-up subjects and establishment of vital status, if needed.

10.4. Interruption of Study Drug

Any study drug interruptions of > 24 consecutive hours during the treatment phase will be recorded in the IRT. The reason for study drug interruption or premature discontinuation of study drug must be documented in the IRT, including discontinuation for hospitalization. If there is any interruption of study drug, subjects should be encouraged to return to treatment as soon as possible.

10.5. Study Termination Criteria

The study may be terminated for any of the following reasons:

1. The local health authority requests a termination of the study.
2. It is determined that the risk level associated with the study drug/device combination therapy is significant and warrants termination of the study.
3. The Sponsor decides to terminate the study.

10.6. Deviations from the Protocol

A protocol deviation is defined as an event where the clinical Investigator or site personnel did not conduct the study according to the protocol or the Investigator Agreement. No deviations from the protocol should be initiated, except when necessary to eliminate immediate hazards to subjects (E6 ICH).

11. STUDY SCHEDULE OF ASSESSMENTS

Enrolled subjects will be required to complete a minimum of 7 study visits (Screening, Baseline [Week 0], Weeks 2, 6, 10, 14, and 18, or until the subject is withdrawn or discontinues from the study. Subjects who discontinue study drug will be encouraged to complete all scheduled study assessments through week 18.

Pre-Screening and Screening Logs will be maintained in IRT for all subjects who do not meet study criteria and for subjects who meet all criteria but do not elect to be enrolled. The Screening Log will contain the site location, subject's demographic data (age, sex), the date subject was seen in the office or clinic, if the subject did or did not meet Inclusion and Exclusion criteria, and if the subject declined enrollment (i.e., did not consent to participate in the study).

Part 1 Screening Visit the following assessments will be performed:

- Informed Consent
- Inclusion/Exclusion
- Medical History
- Prior and concomitant medications
- WHO Functional Class
- 6 Minute Walk Test
  Note: Screening 6MWT may be obtained at baseline if the subject is known to have a 6MWD $\geq$ 100 meters and $\leq$ 450 meters.
- Borg Dyspnea Scale
- Vital Signs including HR, RR, BP and temperature. SpO_2 and methemoglobin via pulse oximetry (O_2 flow rate)
- Total Lung Capacity (only if not performed within 6 months of screening visit)
- Spirometry including DLCO
- Physical Examination including height and weight
- Hematology and Chemistry including pregnancy test (serum or urine)
- BioMarker – NT-proBNP
- Medical Resource Utilization – the number of emergency room and outpatient visits made in the past year
- Lung Transplant Listing Status
- RHC will be conducted at Screening for subjects who meet all other inclusion exclusion criteria, are not participating in the sub-study, and who have not had a RHC within the previous 5 years

Baseline Visit, Week 0, the following assessments will be performed:

- Prior and concomitant medications
- WHO Functional Class
- 6 Minute Walk Test (only if not performed at screening visit)
- Vital Signs including HR, RR, BP and temperature. SpO_2 via pulse oximetry (O_2 flow rate)
- Randomization
- Echocardiogram all subjects
- Complete SF-36
- Assess AEs, SAEs, AESI's
- Medical Resource Utilization
- Lung Transplantation listing status
- Survival Status
- RHC prior to randomization for subjects participating in the RHC substudy
- Drug Device Dispensation

  Instruct and train the subject in the use, maintenance and storage of the following study items: the study drug, study device, and smartphone with its application (app). This will include reviewing the INOpulse instruction guide that explains, step-by-step, how to use the study drug and device, how to care for the study device, how to properly store the study materials and equipment, what to do if there are any problems with the study materials, and whom to contact if the subject has questions. In addition, the subject will be given instructions on how to use the smartphone and its app in order to acknowledge receipt of study materials and scan the study drug used each day.

  After the subject is trained on how to use the study drug and device, the study drug will be started while the subject is in the hospital/clinic.

- Evaluation for symptomatic Rebound Hypertension after start of study drug and prior to sending the subject home as described in Section 11.1.15.

  The study drug will be given while under medical supervision for 1 hour, the study drug will be stopped for 1 hour to make sure the subject does not have any symptoms of rebound pulmonary hypertension before going home. Rebound pulmonary hypertension may occur when inhaled nitric oxide is stopped suddenly.

The subject will be sent home with the working device and breathing the study drug. From that time to the end of the subject's participation in the study, they should wear the device and breathe the study drug as much as possible for up to 24 hours per day with some exceptions (while taking a shower, changing clothes, etc.). Using the study drug/device for as close to 24 hours per day will likely result in the best chance for the optimal effect. The subject will need to agree to use the study device for at least 12 hours each day until the end of the study. The subject will leave the baseline visit with a 1-week supply of study drug. An additional week's supply of study drug will be delivered to the subject's home.

Part 1 Week 2 Visit the following assessments will be performed:

- Prior and concomitant medications
- WHO Functional Class
- Conduct two 6 Minute Walk Tests (the average of the two 6MWD at Week 2 after run-in will be used as the baseline value)
- Borg Dyspnea scale
- Vital Signs including HR, RR, BP and temperature. SpO_2 and methemoglobin via pulse oximetry (O_2 flow rate)
- Assess AEs, SAEs, AESIs
- Medical Resource Utilization
- Lung Transplantation listing status
- Survival assessment
- Completion of the SF-36
- Drug Device Dispensation
- Review Drug Device Usage
- Evaluation for symptomatic Rebound Hypertension while under medical supervision, after start of study drug and prior to sending the subject home as described in section 11.1.15

If the subject does not use the device for an average of at least 12 hours a day, the subject may not be eligible to continue to participate in the study.

If the subject continues to participate, at this visit the subject will be dispensed a 1 week supply of study drug. Additional supplies will be delivered directly to the subject's home. The used cartridges must be returned and will be picked up from the subject's home when the new supplies are delivered.

Part 1 Week 6 (Month 1), Week 10 (Month 2), Week 14 (Month 3) and Week 18 (Month 4) - the following assessments will be performed:

- Prior and concomitant medications
- WHO Functional Class
- Conduct 6 Minute Walk Test
- Borg Dyspnea scale
- Vital Signs including HR, RR, BP and temperature. SpO_2 via pulse oximetry (O_2 flow rate)
- Complete SF-36 (week 18)
- Assess AEs, SAEs, AESIs
- Medical Resource Utilization
- Lung Transplantation listing status
- Drug Device Dispensation (via home delivery)
- Review Drug Device Usage
- Spirometry testing including DLCO (week 18)
- Physical examination (week 18)
- Laboratory – Hematology and Chemistry (week 18)
- NT-proBNP (week 18)

- Pregnancy test (week 18)
- Methemoglobin (week 6)
- INOpulse Questionnaire (week 18)
- RHC subjects participating in the substudy (week 18)
- ECHO – subjects participating in the substudy (week 10 and 18)
- Survival status
- All blinded drug cartridges from Part 1 of the study must be returned to the site or Sponsor prior to dispensing open-label drug cartridges for Part 2.

Part 1 Early Term: The following visit assessments will be performed:

- Prior and concomitant medications
- WHO Functional Class
- Conduct 6 Minute Walk Tests
- Borg Dyspnea scale
- Vital Signs including HR, RR, BP and temperature. SpO2 and methemoglobin via pulse oximetry (O2 flow rate)
- Complete SF-36
- Assess AEs, SAEs, AESIs
- Medical Resource Utilization
- Lung Transplantation listing status
- Review Drug Device Usage
- Spirometry testing including DLCO
- RHC for subjects participating in substudy
- ECHO (for safety assessment) for ALL subjects including those not participating in ECHO substudy
- Physical examination
- Laboratory – Hematology and Chemistry
- Methemoglobin
- Pregnancy test
- Survival status
- All blinded drug cartridges from Part 1 of the study must be returned to the site or Sponsor.

Assessments Part 2

Part 2 Week 0 Visit: The following Assessments will be performed:

- Informed Consent
- Methemoglobin via pulse oximetry (O_2 flow rate)
- Drug Device Dispensation for Open Label treatment
    - If the subject continues to participate, at this visit the subject will be dispensed a 1 week supply of study drug. Additional supplies will be delivered directly to the subject's home every 4 weeks. The used cartridges must be returned and will be picked up from the subject's home when the new supplies are delivered.

- Pregnancy test (at the discretion of the investigator)
- Evaluation for symptomatic Rebound Hypertension while under medical supervision, after start of study drug and prior to sending the subject home as described in section 11.1.15

Part 2 Week 2 Visit is a Telephone Visit:

Study Staff will contact the subject via telephone call and the following assessments will be completed:

- Review of prior and concomitant medications
- Assessment of AE,SAEs, AESI

Part 2: Week 16, Week 32, and Week 52 Visits - the following assessments will be performed:

- Prior and concomitant medications
- WHO Functional Class
- Conduct 6 Minute Walk Test
- Borg Dyspnea Scale
- Laboratory – Hematology and Chemistry (Week 52 only)
- Pregnancy test (at the discretion of the Investigator)
- Vital Signs including HR, RR, BP and temperature. SpO_2 and methemoglobin (Week 52 only) via pulse oximetry (O_2 flow rate)
- Assess AEs, SAEs. AESIs
- Drug Device Dispensation (every 4 weeks via home delivery)
- Review Drug Device Usage
- Evaluation for symptomatic Rebound Hypertension while under medical supervision, after start of study drug and prior to sending the subject home as described in section 11.1.15

Part 2: Every 4 Month Visits: The following assessments will be performed:

- Prior and concomitant medications
- Assessment of AEs, SAEs, AESI
- Vital signs: BP and HR, SpO2 and methemoglobin via pulse oximetry (annually)
- Review device usage with the subject
- Laboratory – Hematology and Chemistry will be conducted on a yearly basis (Pregnancy testing will be left to the discretion of the Investigator)
- Drug Device Dispensation (every 4 weeks via home delivery)

Part 2: End of Study (EOS) or Early Discontinuation- The following assessments will be performed:

- Prior and concomitant medications

- Assessment of AEs, SAEs, AESI
- Vital signs: BP and HR, SpO2 and methemoglobin via pulse oximetry.
- Review device usage with the subject
- Laboratory – Hematology and Chemistry (pregnancy testing will be left to the discretion of the Investigator)
- Final Drug Device Usage download

Table 2 Presents the Schedule of Assessments to be performed for Parts 1 & 2.

Table 2: Part 1 : Schedule of Assessments

	Screening	**Run in**		**Blinded Treatment Period**				
Assessment	**Screening**	**Baseline Week 0** Within 28 days of screening visit	**Week 2** (±3 days)	**Week 6 Month 1** (± 7 days)	**Week 10 Month 2** (±7 days)	**Week 14 Month 3** (± 7 days)	**Week 18 Month 4** (±7 days)	**Early D/C**
Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Medical History	X							
Prior and Concomitant Medications	X	X	X	X	X	X	X	X
WHO Functional Class	X	X	X	X	X	X	X	X
6 Minute Walk Test	X	X[a]	X[a]	X	X	X	X	X
Borg Dyspnea Score, Heart Rate and SpO_2	X		X	X	X	X	X	X
Vital Sign Measurements (includes SpO_2 via pulse oximetry)	X	X	X	X	X	X	X	X
Total Lung Capacity (TLC)	X[b]							
Spirometry Testing (and DLCO)	X[c]						X	X
Physical Examination	X[d]						X	X
Pregnancy test	X						X	X
MetHgb	X		X	X				X

Hematology, Chemistry	X						X	X
NT-proBNP	X						X	
Eligibility for INOpulse (average daily use ≥ 12 hr/day)			X[h]					
Randomization		X						
Right Heart Catheterization (subset of ~50 subjects)		X					X	X[i]
Right Heart Catheterization (all subjects not enrolled in subset)	X[j]							
Echocardiogram for central reading (subset of ~50 subjects)		X			X		X	X[i]
Echocardiogram for local reading only (all subjects not enrolled in subset)		X						X[i]
Evaluation for Symptomatic Rebound PH		X[k]	X					
Patient Reported Outcomes (SF-36)		X					X	X
AEs/SAEs/AESIs		X	X	X	X	X	X	X
Drug Dispensing for Run-in period		X[l]						
Drug Dispensing for blinded treatment period			X[l]	X[l]	X[l]	X[l]		
Drug/Device Usage[n]			X[n]	X[n]	X[n]	X[n]	X[n]	X[n]
INOpulse Questionnaire							X[m]	X
Survival Assessment		X	X	X	X	X	X	X
Medical Resource Utilization	X	X	X	X	X	X	X	X
Lung Transplantation Listing Status	X	X	X	X	X	X	X	X

[a] Screening 6MWT may be obtained at baseline if the subject is known to have a 6MWD ≥ 100 meters and ≤ 450 meters. The average of the two 6MWD at Week 2 after run-in will be used as the baseline value

[b] Total lung capacity test to be done if not performed within 6 months of Screening.

[c] DLCO (diffusing capacity for the lungs measured using carbon monoxide).

[d] Height and weight to be performed at Screening.

[e] N/A-Footnote no longer applicable as of Amendment #

[f] Pregnancy testing to be performed at the discretion of the Investigator.

[g] N/A-Footnote no longer applicable as of Amendment #3

[h] Subjects will be required to demonstrate an average daily usage ≥ 12 hours (rounded to the nearest hour) with no more than 2 days of usage < 8 hours per day of the INOpulse device during the initial 2 weeks of the study in order to be eligible to continue to the treatment phase.

[i] RHC should be obtained at early discontinuation only for subjects participating in RHC substudies ECHO should be obtained for all subjects at early discontinuation regardless if they are participating in the ECHO substudy.

[j] A RHC will be conducted at Screening for subjects who are not included in this subset who have not had a RHC within the previous 5 years that meet eligibility criteria and are otherwise eligible. See Section 11.1.13 for full RHC assessments.

[k] After randomization at Week 0 and at end of Run-in, Week 2, all subjects will remain in the hospital or clinic under medical supervision for 1 hour after starting study drug and for 1 hour after study drug is discontinued for observation for signs and symptoms of rebound PH. Vital signs, including heart rate, respiratory rate, blood pressure, and SpO_2 will be recorded in the supine position every 15 minutes for 1 hour, and then again every 15 minutes for another hour after discontinuation of study drug. After the 1 hour observation period off study drug, if the subject's status is unchanged with respect to vital signs and symptoms and subject does not exhibit signs or symptoms of rebound PH, they will restart their blinded study drug treatment and be sent home.

[l] One week of drug dispensed to site at Baseline and Week 2; all other drug dispensed to subject's home via home delivery

[m] At Week 18 or prior to study discontinuation

[n] Site personnel should review INOpulse use with the subjects during study visits to encourage use as close to 24 hours per day as possible. Reasons for device interruptions should also be reviewed with the subject.

Table 2 Part 2 Assessment Table:

Part 2			**Open-Label Long Term Extension Period**				
Assessment	**Week 0** If subject enters Part 2, Week 0 assessments are done at Week 18 of Part 1	**Week 2** +/- 3 days (phone call)	**Week 16 Month 4** +/-14 days	**Week 32 Month 8** +/-14 days	**Week 52 Month 12** +/-14 days	**Every 4 Months until EOS** +/-14 days	**EOS (or Early D/C**
Informed Consent	X[1]						
Inclusion/Exclusion Criteria	X[2]						
Review of Prior and Concomitant Medications		X	X	X	X	X	X
WHO Functional Class			X	X	X		
6 Minute Walk Test			X	X	X		
Borg Dyspnea Score, Heart Rate and SpO_2			X	X	X		
Vital Sign Measurements (includes SpO_2 via pulse oximetry)			X	X	X	X	X
Telephone contact		X					
Pregnancy test	X[4]		X[4]	X[4]	X[4]	X[4]	X[4]
MetHgb	X				X	X[5]	X
Hematology, Chemistry					X	X[5]	X

Evaluation for Symptomatic Rebound PH	X[6]		X	X	X		
AEs/SAEs/AESIs		X	X	X	X	X	X
Drug Dispensing for Open Label Extension	X[1]		X[7]	X[7]	X[7]	X[7]	
Drug/Device Usage			X[8]	X[8]	X[8]	X[8]	X[8]

[1] Ensure the subject has agreed to participate in both parts of the PAH-004 study by checking and initialing Part 1 & Part 2 participation in the ICF

[2] Subject must have completed 18 weeks of blinded treatment

[3] N/A-Footnote no longer applicable as of Amendment #3

[4] Pregnancy testing to be performed at the discretion of the Investigator.

[5] Hematology and chemistry labs and MetHgb will be performed on a yearly basis.

[6] Assessment Symptomatic Rebound PH: all subjects will remain in the hospital or clinic under medical supervision for 1 hour after starting study drug and for 1 hour after study drug is discontinued for observation for signs and symptoms of rebound PH. Vital signs, including heart rate, respiratory rate, blood pressure, and SpO_2 will be recorded in the supine position every 15 minutes for 1 hour, and then again every 15 minutes for another hour after discontinuation of study drug. After the 1 hour observation period off study drug, if the subject's status is unchanged with respect to vital signs and symptoms and subject does not exhibit signs or symptoms of rebound PH, they will restart their blinded study drug treatment and be sent home.

[7] One week of Open Label Drug dispensed by site at Week 0; all other drug dispensed to subject's home via home delivery every 4 weeks thereafter

[8] Site personnel should review INOpulse use with the subjects during study visits to encourage use as close to 24 hours per day as possible. Reasons for device interruptions should also be reviewed with the subject.

11.1. Details of Study Assessments

11.1.1. Informed Consent

At Screening, each subject (or legally authorized representative) must provide informed consent in writing after having had adequate time to ask questions and consider his/her participation in this study. Consent must be obtained prior to any protocol related procedure or assessment that is not part of the subject's normal care. Subjects will indicate if they are consenting to participate in both parts of the PAH-004 study by checking and initialing Part 1 & Part 2 participation in the ICF. Participating centers will be responsible for assuring that written informed consent is

provided by each subject using an informed consent form (ICF) approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) granting approval for the conduct of the study. Documentation of IRB or IEC approval for the conduct of the study and the ICF must be provided to Bellerophon Pulse Technologies LLC or its designee.

11.1.2. Medical History

At Screening, relevant medical history and demographics (sex, race, and ethnicity) will be assessed.

11.1.3. Prior and Concomitant Medications

All prior and concomitant medications, including all over-the-counter medications, will be recorded in Part 1 at Screening, Baseline, Weeks 2, 6, 10, 14, and 18 including early discontinuation. In Part 2, at Week 2, Week 16, Week 32, Week 52, Every 4 months and Early Discontinuation/End of Study.

11.1.3.1. Diuretic Use

In Part 1 at each study visit, the dose of any diuretic use should be recorded in the eCRF, including spironolactone.

11.1.3.2. PAH Specific Therapies

Specific attention will be paid to PAH specific and supporting therapies. Each dose of any specific PAH therapy should be recorded, including ERA, PDE-5 inhibitor, prostacyclin or a prostacyclin analog. If addition of riociguat is required, the subject will need to be discontinued from study drug, but should remain in study and complete all assessments until EOS. Increases in prostanoid dose may be necessary over the length of the study due to tachyphylaxis and will not be considered a TTCW event. The addition of prostanoid therapy or increases in prostanoid dose as a TTCW event will be determined by the ICEC.

LTOT flow rates should be kept constant throughout the study unless the subject has persistent desaturations to less than 88% of SpO_2, or otherwise clinically indicated. LTOT flow rate with the estimated length of use per day must be documented in the eCRF at all visits.

11.1.4. WHO Functional Class

WHO Functional Class assessment, as defined in Table 3, will be assessed by the clinical Investigator in Part 1 at Screening, Baseline, Weeks 2, 6, 10, 14, and 18, including early discontinuation In Part 2 at Week 16 and 32 and 52.

Table 3: WHO Functional Classification

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

Class II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity. Syncope or near syncope may occur.

*Only subjects with WHO Class II –IV are eligible for the study

11.1.5. 6 Minute Walk Test

In Part 1, a standard 6MWT will be performed at Screening, Weeks 6, 10, 14, and 18, including early discontinuation , and **two** 6MWTs at Week 2 as presented in the ATS guidelines (ATS Statement 2002; Appendix A). The Screening 6MWT may be obtained at baseline if the subject is known to have a 6MWD ≥ 100 meters and ≤ 450 meters. The average of the two 6MWD at Week 2 after run-in will be used as the baseline value. The subject should rest for at least 30 minutes between tests.

All 6MWTs, including those at Screening, Baseline, and post-randomization visits, should be performed in the same manner for each subject. Each subject will be provided with a carrying case with straps that will allow the device to be attached to the oxygen cylinder. During the 6MWT all subjects will be placed on oxygen at a continuous flow rate as prescribed by treating physician using an oxygen cylinder that is on a wheeled carrier. All subjects must pull the oxygen tank with the INOpulse device attached to the cylinder during all 6MWTs. Flow rate must be recorded in eCRF.

The subject should use the same oxygen tank and cart as well as the same flow rate during ALL subsequent 6MWTs, Part 1 and Part 2. If a change in the subject's oxygen supplementation is clinically indicated during the 6MWT, then during all subsequent 6MWTs the subject should use the same increased amount of LTOT administered in the same concentration or flow rate. Change in flow rate should be recorded in the eCRF.

At Screening 6MWT should be performed on oxygen with INOpulse device (turned off) attached to oxygen tank. At Week 2 6MWT should be performed on oxygen plus INOpulse device set at 15 mcg/kg IBW/hr and attached to oxygen tank.

All 6MWTs after Week 2 should be performed on oxygen plus INOpulse device set at 75 mcg/kg IBW/hr and attached to oxygen tank

In Part 2, the 6MWT will be performed at only Week 16, Week 32, and Week 52 on oxygen plus INOpulse device set at 75 mcg/kg IBW/hr and attached to oxygen tank.

11.1.6. Borg Dyspnea Scale

The Borg Dyspnea Scale, Heart Rate and SpO_2 will be recorded in Part 1 at each study visit prior to, and immediately following, the 6MWT at Screening, Weeks 2, 6, 10, 14, and 18, including early discontinuation (ATS Statement 2002) and in Part 2, at week 16, week 32 and week 52. The BDS measures perceived breathlessness on a scale of 0 (none) to 10 (maximum) and has a minimally clinically important difference (MCID) of 1 point (Table 4) (Ries 2005).

Table 4: Borg Dyspnea Score

Score	Severity
0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	---
7	Very severe
8	---
9	---
10	Very, very severe (maximal)

11.1.7. Vital Sign Measurements

Vital sign measurements will be performed for Part 1 at Screening, Baseline, Weeks 2, 6, 10, 14, and 18, including early discontinuation. Vital sign measurements will include heart rate (HR), respiratory rate (RR), blood pressure (BP, systolic and diastolic), and temperature. Oxygen flow rate will be recorded at each visit with estimated length of use per day.

Systemic arterial oxygenation (SpO_2) will be performed in Part 1 at Screening, Baseline, Weeks 2, 6, 10, 14, 18, and at any time of an early drug discontinuation:

- While breathing room air for at least 5 minutes
- While breathing prescribed oxygen flow rate for at least 5 minutes

- While breathing prescribed oxygen flow rate with study device/drug for at least 5 minutes to be conducted **after** week 2 (not at screening or baseline), at Week 6 through Week 18 or Early Discontinuation

In Part 2 – Vital signs and Systemic arterial oxygenation will be performed in Part 2 at Week 16, Week 32, Week 52 and Every 4 months and Early Discontinuation/End of Study.

11.1.8. Spirometry Testing and DLCO

Spirometry testing with DLCO will be assessed in Part 1 at Screening, and Week 18 and at any time of an early drug discontinuation before Week 18, and will include absolute value and percent predicted value of forced vital capacity [FVC], forced expiratory volume at 1 second [FEV_1], FEV_1/FVC ratio and DLCO.

Pulmonary Function Measurements

1. Spirometer provided for this study has to be calibrated and maintained to acceptable respiratory function standards (Miller 2005).
2. Forced-spirometry PFTs will be repeated up to 8 times to obtain 3 acceptable readings according to ATS/ERS 2005 spirometry guidelines.
3. Forced-spirometry repeatability is achieved when the difference between the largest and the next largest FVC is ≤ 150 ml and the difference between the largest and the next largest FEV_1 is ≤ 150 ml. For subjects with an FVC of ≤ 1.0 L, both these values are 100 ml.
4. Total lung capacity (TLC), if results not obtained in the last 6 months, should be obtained according to ATS/ERS 2005 guidelines.
5. DLCO (diffusing capacity for the lungs measured using carbon monoxide) will be performed at Screening and Week 18, and at any time of an early drug discontinuation before Week 18. (according to ATS/ERS 2005 spirometry guidelines).

11.1.9. Physical Examination

A physical examination, including height and weight, will be performed in Part 1 at Screening to determine IBW. Physical examinations, including weight, will be performed at Week 18, and at any time of an early drug discontinuation before Week 18. A physical examination will not be required for Part 2.

11.1.10. Pregnancy Test

A pregnancy test will be performed in Part 1 at Screening Week 18, and at any time of an early drug discontinuation before Week 18. In Part 2, pregnancy testing is at the discretion of the Investigator.

Females of childbearing potential must have a negative serum or urine pregnancy test at Screening. All female subjects should take adequate precaution to avoid pregnancy by using highly effective birth control methods which include (as outlined in CTFG Contraceptive Recommendations Section 4.1):

- Combined (estrogen and progestogen containing) hormonal contraception associated

with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
    - oral
    - injectable
    - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence

11.1.11. Hematology, Chemistry, Methemoglobin, NT-proBNP

Hematology laboratory tests will be performed in Part 1 at Screening and Week 18, and at any time of an early drug discontinuation before Week 18. These laboratory tests will include complete blood count (CBC) with differential and platelet count. In Part 2 will be performed at Week 52, yearly and at End of Study or Early Discontinuation.

Chemistry laboratory tests will be performed in Part 1 at: Screening and Week 18, and at any time of an early drug discontinuation before Week 18.

In Part 2, Hematology and Chemistry laboratory tests will be performed at Week 52, then on a yearly basis until EOS, or Early Discontinuation. These laboratory tests include: electrolytes (Na, K, HCO_3, and Cl), glucose, blood urea nitrogen (BUN), creatinine (Cr), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), magnesium, bilirubin total/direct, uric acid, total protein, and albumin.

Methemoglobin levels (%) will be measured by oximetry in Part 1 at Screening and Week 2, Week 6 and at any time of an early drug discontinuation before Week 18. In Part 2 will be performed at Week 0, Week 52 and yearly including EOS or early discontinuation

NT-proBNP will be collected in Part 1 at Screening and Week 18. NT-proBNP will not be collected in Part 2

11.1.12. Eligibility of INOpulse Device Usage

Subjects will be required to demonstrate an average daily usage ≥ 12 hours (rounded to the nearest hour) with no more than 2 days of usage < 8 hours per day of the INOpulse device during the initial 2 week run-in period of the study in order to be eligible to continue to the treatment phase. Calculation of compliance: First day and last day's data during the run-in period does not count towards compliance data. This assessment will occur during the Run-in period at Week 2 in Part 1.

11.1.13. Right Heart Catheterization

A RHC may be performed under the following circumstances in Part 1:

- A RHC will be performed in a subset of approximately 50 subjects at selected sites. The RHC performed at Baseline will be used as entrance criteria. A repeated RHC will be performed at Week 18 to assess changes in pulmonary hemodynamics. RHC at Week 18 should be performed while the subject is in stable condition and on study drug for at least 30 minutes prior to the start of the procedure.
- For subjects who are not included in this subset who have not had a RHC within the previous 5 years that meet eligibility criteria and are otherwise eligible, a RHC will be conducted at Screening.
- Subjects in the subset who discontinue study drug prior to Week 18 will have a RHC performed at time of study drug discontinuation rather than Week 18..

11.1.13.1. RHC Procedure

Hemodynamic stability will be established prior to recording baseline hemodynamic data and at Week 18 or early discontinuation in Part 1

Cardiac output (CO) will be determined by thermodilution (in triplicate). For each CO, PAP S/D/mean; SAP S/D/mean; mRAP; mPCWP or LVEDP, SpO_2, and mixed venous oxygen saturation (blood sample from tip of PA catheter when not in the wedge position) will also be measured. The average of the triplicate measurements will be used in the data analysis. The CO measurements must be within 15% of one another. To determine if the individual values are within 15% of one another, PAP S/D/mean; SAP S/D/mean; mRAP; mPCWP and LVEDP must be measured at end-expiration. All measurements will be recorded in the eCRF.

Important Note: The transducer must be leveled at the mid-axillary line at the level of the mid-sternum (half way between the mid-sternum and table top). The distance of the mid-axillary line from the table top must be recorded in the eCRF for the Baseline, Week 18, or any RHC performed at the time of study drug discontinuation. The transducer must be leveled to the same height at the baseline RHC and for all subsequent RHC.

Cardiac output must be performed only by thermodilution or Continuous Cardiac Output (CCO). Iced or room temperature saline may be used. The methods used for measurement should be maintained for all RHC and recorded in the eCRF.

Acute Vasoreactivity Testing

AVT will be performed after Baseline RHC measurements are completed and prior to randomization in all subjects at selected centers that will perform RHC in Part 1 if possible. AVT testing with iNO is preferred if available at the site. If not available, the site may use other means of AVT that are part of clinical care at the site. RHC must be performed as described in Section 11.1.13.1. Measurements must be performed in triplicate after stabilizing the subject on oxygen at a flow rate to maintain SpO_2 at $\geq$ 90% plus iNO 40 ppm for at least 5 minutes. Exposure RHC measurements will be recorded in the eCRF. Data recorded will include iNO dose (ppm) and duration of iNO exposure (minutes) or dose of alternative agent used for AVT and duration of exposure. A responder to AVT with iNO is defined as a decrease in mPAP by $\geq$ 10 mmHg to an absolute level of < 40 mmHg without a clinically significant decrease in CI.

11.1.13.1.1. Anesthesia

If either moderate sedation or general anesthesia is used at the Baseline RHC in Part 1, the same sedation or anesthesia should be used for subsequent RHCs.

11.1.13.1.2. LTOT

The same flow rate of LTOT should be used during all RHCs unless a greater concentration of oxygen is needed for medical reasons. LTOT levels must be recorded in the eCRF. Reasons for any change in oxygen use should be documented.

11.1.13.2. Hemodynamic Calculations

The following calculations will be used to determine hemodynamic and pharmacodynamic endpoints:

CI will be calculated according to the formula:

CI (L/min/m^2) = CO ÷ BSA

where CO = cardiac output (L/min), and BSA (body surface area) (m^2) = 0.007184 * (weight $^{0.425}$) * (height $^{0.725}$) with weight expressed in kg and height in cm

PVR will be calculated according to the formula:

PVR (dyn·sec/cm^{-5}) = 80 (mPAP - mPCWP) ÷ CO

where mPAP = mean pulmonary artery pressure (mmHg), mPCWP = mean pulmonary capillary wedge pressure (mmHg), and CO = CO (L/min)

SVR will be calculated according to the formula:

SVR (dyn·sec/cm^{-5}) = 80 (mSAP - mRAP) ÷ CO

where mSAP = mean systemic arterial pressure (mmHg), mRAP = mean right atrial pressure (mmHg), and CO = CO (L/min)

TPR will be calculated according to the formula:

TPR (dyn·sec/cm^{-5}) = 80 (mPAP ÷ CO)

where mPAP = mean pulmonary artery pressure (mmHg) and CO = CO (L/min)

11.1.14. Echocardiogram

An echocardiogram will be performed in Part 1 on a subset of approximately 50 subjects at selected sites at Baseline, Week 10, Week 18, and any time a subject discontinues treatment prior to week 18. Subjects who have discontinuation of study drug will undergo echocardiography at the time of discontinuation.

Echocardiographic measures will include right ventricular function (systolic pulmonary artery pressure [sPAP], fractional area change of the right ventricle, tricuspid annular motion/tricuspid annular plane systolic excursion, tricuspid annular systolic velocity, and Tei index) and left ventricular function (including left ventricular ejection fraction [LVEF], LV size, and

improvement in LV early diastolic relaxation velocity). All echocardiograms will be supervised, collected, and evaluated by a central core laboratory.

For all other subjects not enrolled in the echocardiogram subset, a local echocardiogram will be obtained at baseline and at any time the subject discontinues treatment prior to week 18 as a safety endpoint. Results of PASP, RVEF, and LVEF will be recorded in the eCRF in Part 1.

Site Preparation, Sonographer Training and Certification

Site instruction manual

The central core laboratory will prepare a Site Instruction Manual (SIM) designed to provide study sites information regarding:

- The required echo views to obtain
- Instructions on how to optimize images for obtaining high quality views, to complement sonographer training with central core laboratory staff and serve as a real-time reference
- Instructions on how to send echo images to the Cardiac Imaging Core Lab for analysis.

Sonographer training

Training will be provided by the Cardiac Imaging Core Lab.

Sonographer certification

Each site will be asked to designate specific sonographer(s) to perform all study echocardiograms. Following training, each site sonographer will be required to submit 1 sample study performed per study protocol. Studies will be scrutinized for adherence to protocol, acquisition of all required views, and image quality. Itemized direct written feedback and suggestions from the central vendor will be provided. Sonographers will have the opportunity to resubmit a sample protocol study. Following submission of an adequate sample study, site sonographer will be officially certified, with written documentation.

11.1.15. Evaluation for Symptomatic Rebound Pulmonary Hypertension

In Part 1, after randomization at Week 0 and at end of Run-in, Week 2, all subjects will remain in the hospital or clinic under medical supervision for 1 hour after starting study drug and for 1 hour after study drug is discontinued for observation for signs and symptoms of rebound PH (see Section 15.1.5). Vital signs, including heart rate, respiratory rate, blood pressure, and SpO_2 will be recorded in the supine position every 15 minutes for 1 hour, and then again every 15 minutes for another hour after discontinuation of study drug.

At Week 0, INOpulse device should be set at 15 mcg/kg IBW/hr. At Week 2 the evaluation will be performed with the INOpulse device reset to 75 mcg/kg IBW/hr

In the opinion of the Investigator, subjects who develop clinically significant signs and/or symptoms consistent with rebound PH (e.g., systemic hypotension, change in heart rate, new onset syncope, or decreased systemic oxygenation) temporally associated with acute withdrawal, and including those associated with device malfunction or failure, will be discontinued from study treatment and not replaced (see Section 10).

In Part 2 evaluation should be performed at Week 0, Week 16 and Week 32 and Week 52.

During Part 2 if the subject develops clinically significant rebound PH, the subject may continue on open label therapy if it is considered in the opinion of the investigator to be in the subject's best interest.

The final diagnosis of rebound PH will be adjudicated by an ICEC. The DMC will review the data for subjects enrolled in the study and evaluated for rebound PH (including the ICEC adjudication) and make a decision whether or not to continue evaluation for rebound PH and/or to determine additional steps required in order to maintain subject safety.

After the 1 hour observation period off study drug, if the subject's status is unchanged with respect to vital signs and symptoms and subject does not exhibit signs or symptoms of rebound PH, they will restart their blinded study drug treatment and be sent home.

11.1.16. Patient Reported Outcomes

Collection of data for both general and disease-specific patient reported outcome measurements will be administered during Part 1 at Baseline, Week 18, including and at any time of an early drug discontinuation before Week 18. These are not collected during Part 2.

11.1.16.1. SF-36

The SF-36V2 health survey is a widely used, multi-dimensional, validated health related quality of life (HRQoL) questionnaire designed to measure dimensions of general, physical, and mental health in large populations, with scores ranging from 0 to 100. The questionnaire yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Accordingly, the SF-36 health survey has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments. It consists of eight multi-item domains combined to provide the following two summary scores: the physical component summary, composed of physical functioning, role-physical, bodily pain, and general health domains; and the mental component summary, composed of role-emotional, mental health, social functioning, and vitality domains.

11.1.17. Adverse Events

Adverse events, including AESIs and serious AEs, will be assessed in Part 1 at Baseline, Weeks 2, 6, 10, 14, and 18, including and at any time of an early drug discontinuation before Week 18 If an AE, SAE or AESI occurs while the subject is at home, then either the subject, the subject's caregiver or family member, or other responsible person will contact the study coordinator or Investigator at the research site and that person will record, assess, and report the event as indicated. In Part 2 at Week 2, Week 16, Week 32, Week 52, every 4 months and Early Discontinuation/End of Study

11.1.17.1. Adverse Events of Special Interest

AESIs will include all respiratory related AEs, epistaxis, syncope and rebound PH. All SAEs, and rebound PH will be adjudicated (see also Section 15.7).

At each visit, subjects should be queried on all AESIs. Respiratory AEs should be specifically sought out. Subjects should be comprehensively queried for, e.g., hospitalization for any reason, pulmonary infections, important increases in chronic pulmonary medications, dyspnea, cough, hypoxia, acute respiratory failure, bronchitis, epistaxis, syncope including pre-syncope and loss of consciousness (new onset, or if history of syncope, recurrent syncope events), signs and symptoms of rebound PH and any other respiratory related AEs. These queries are to be documented in the eCRF on a separate page dedicated to AESIs. The severity of all AEs (AESI and non-AESI), treatment given, hospitalization required, and duration in number of days should be recorded in the AE section of the eCRF.

11.1.18. Drug Dispensing for Run-in Period

When a subject enters the Run-in period, the site will provide the subject with two INOpulse devices (a primary and a back-up), and at least a 1 week supply of study drug and ancillary supplies assigned by the Interactive Response Technology (IRT) system. The subject will also be given a handheld mobile device to be used to capture drug accountability.

In addition, the Week 2 drug supply will be shipped directly to the subject's home to ensure the subject is able to receive and acknowledge shipments of drug supplies.

Details of the home delivery will be outlined in the study specific Distribution Plan document.

11.1.19. Drug Dispensing for Blinded Treatment Period (Part 1)

When a subject is enrolled in the blinded treatment period of the study, the site will provide the subject with two INOpulse devices (a primary and a back-up), and at least a 1 week supply of study drug and ancillary supplies assigned by the IRT.

All additional treatment period drug supply will be shipped directly to the subject's home.

Details of the home delivery will be outlined in the study specific Distribution Plan document.

11.1.20. Drug Dispensing for Open Label Long Term Extension (Part 2)

When a subject is enrolled in the open label long term extension of the study, the site will continue to provide the subject with two INOpulse devices (a primary and a back-up), a 1 week supply of study drug and ancillary supplies assigned by the IRT.

All additional treatment period drug supply will be provided directly to the subject's home.

Details of the home delivery will be outlined in the study specific Distribution Plan document.

No study drug supplies for Part 1 can be used for Part 2 of the study. All supplies for Part 1 must be returned, new supplies for Part 2 will be provided to the patient.

11.1.21. Drug/Device Usage

Treatment usage will be automatically monitored by the INOpulse device. At each treatment visit in Part 1 and Part 2, including early discontinuation and EOS, site research team personnel will

upload the usage data from the INOpulse device to the data server. This data may also be reviewed with the subject. In the event that the INOpulse device is returned to the Sponsor rather than the site, the usage data will be uploaded by the Sponsor or designee, and the site will be alerted to the upload. Subjects should be encouraged to use the study drug/device as close to 24 hours per day as possible. Subjects should be encouraged to wear the device and breathe the drug as much as possible while sleeping, while at home, and during daytime activities.

11.1.22. INOpulse Device Questionnaire

In Part 1, at the Week 18 visit, or at time of early discontinuation prior to week 18, each subject will be asked to complete a brief questionnaire regarding the usability of the INOpulse device.

11.1.23. Survival Assessment

If a subject is unable to be seen in the clinic for study assessments, then a survival form should be completed for each visit that the subject is not seen in Part 1, including early discontinuation.

11.1.24. Medical Resource Utilization

For the purpose of economic evaluation of the use of iNO as compared to placebo, medical healthcare resource utilization (HRU) will be recorded in Part 1.

At Screening, subjects will be asked about the number of hospitalizations, ER visits, and outpatient visits in the previous year. At each visit thereafter, the Investigator will record the subject's HRU in terms of number of hospitalizations and outpatient medical care, including ER visits, since the previous scheduled visit. The collection of HRU will continue through EOS.

A hospitalization is defined as any visit to the hospital requiring an overnight stay. The frequency and duration of any inpatient hospitalization will be recorded along with the primary reason for the hospitalization and the primary and secondary diagnosis at discharge. For each hospitalization, the duration spent in each of the following will be recorded: intensive care unit, general ward, emergency room, other, along with the type of physician consulted.

The frequency of unscheduled outpatient visits will be recorded along with the type of provider and type of facility visited, including the ER. An unscheduled outpatient visit is defined as any visit with a medical practitioner, in the office or at home, apart from the study visits.

Additionally, any procedures conducted during hospitalization or unscheduled outpatient visits will be recorded in the eCRF.

HRU forms should be reviewed by the Investigator for potential AEs. If AEs or SAEs are confirmed, then the Investigator must record the events as per instructions given in Section 15.1 of the protocol.

11.1.25. Lung Transplantation Listing Status

Subjects on active lung transplant lists will be recorded in the eCRF. At each study visit in Part 1, including early discontinuation, the status of the subject on an active lung transplant list (i.e., not on list, on active list, undergone lung transplantation, removed from active list, died while awaiting transplant) will be recorded in the eCRF. If the subject is removed from an active transplant list during the study, the reason for removal must be recorded in the eCRF. Vital status

must be determined 30 days after lung transplantation. Lung transplant assessments will not be performed in Part 2.

12. INVESTIGATIONAL STUDY DRUG AND DEVICE

12.1. Rationale for Study Design and Dose

The proposed study design allows for determination of whether or not the drug/device combination therapy of iNO at a pulsed dose of 75 mcg/kg IBW/hr delivered via the INOpulse device is effective and well-tolerated. In the Part 2 Open Label Treatment, long term safety data will be collected and will allow subjects who benefit from iNO to continue to receive therapy.

Subjects randomized to active study treatment will receive iNO at 75 mcg/kg IBW/hr for up to 24 hours/day until week 18 or early drug discontinuation before Week 18 via the INOpulse device in a blinded manner.

Placebo, consisting of nitrogen (N2, 99.999%) gas, will be administered for up to 24 hours/day until EOS via the INOpulse device in a blinded manner at 75 mcg/kg IBW/hr device setting.

Subjects on open label treatment will receive iNO at a pulsed dose of 75 mcg/kg IBW/hr delivered via the INOpulse device.

12.2. Description of Study Drug and Device

12.2.1. Inhaled Nitric Oxide

The active study drug, iNO, Nitric oxide for inhalation will be supplied in size 0.074 liter aluminum cartridges at a concentration of 6.0 mg/L (4880 ppm).

Placebo to match study drug will be supplied in size 0.074 liter aluminum cartridges containing nitrogen (N2, 99.999%) gas.

Both the nitric oxide and placebo cartridges will be labeled to maintain the blind.

All subjects will change cartridges in the INOpulse device approximately every 12 hours (see INOpulse Instruction for Use), and document the cartridge change in the IRT (see Section 13.3).

12.2.2. INOpulse Device Description and Operation

The INOpulse Instruction for Use Guide provides complete guidance on the features of the INOpulse device.

12.2.3. Traveling with iNO/INOpulse Combination Therapy

For any travel longer than 24 hours, the subject should be instructed to take a second INOpulse device and at least 48 hours' worth of supplies (i.e., study drug cartridges, cannulae). Each cartridge should last approximately 12 hours during use. Subjects should be instructed to have enough supplies in case of travel delays, and to make sure the INOpulse device battery is fully charged. A fully charged battery will provide power for about 16 hours.

Extended travel will be evaluated on a case-by-case basis and instructions will be provided by the Sponsor.

12.3. Study Drug Administration

There will be 2 dosing cohorts with 94 subjects in each cohort. Dosing regimen during the treatment phase will be via the INOpulse device as shown in Table 5 below.

Table 5: Dosing Regimen via INOpulse Device

Cohort	Number of Subjects	Dosing Regimen via INOpulse Device
Part 1:Cohort 1: Placebo	94	Placebo at a dose setting of 75 mcg/kg IBW/hr for up to 24 hr/day 99.999% Nitrogen [N2] cartridge; change approximately every 12 hours
Part 1:Cohort 2: iNO 75 mcg/kg IBW/hr	94	iNO at a dose setting of 75 mcg/kg IBW/hr for up to 24 hr/day 6.0 mg/L [4800 ppm] NO cartridge; change approximately every 12 hours
Part 2: Open Label	Approx. 150	iNO at a dose setting of 75 mcg/kg IBW/hr for up to 24 hr/day 6.0 mg/L [4800 ppm] NO cartridge; change approximately every 12 hours

*Note: Study drug is dosed according to IBW and not actual body weight. IBW is determined by a subject's sex and height and therefore will not change during the study period.

Study drug should be started after the all Inclusion and Exclusion criteria are met, and following randomization.

12.4. Packaging and Labeling of Study Products

Study drug, device and cannula will be provided by Bellerophon Pulse Technologies LLC. and clinical packaging and labeling will be done by a third party vendor with all legal and regulatory requirements of each country in which the study is being performed.

12.5. Storage, Dispensing, and Accountability of Investigational Study Products

12.5.1. Storage

The study drug is to be stored in accordance with the storage/temperature requirements specified on the study drug labels. The INOpulse device should be stored within the recommended operating conditions specified in the INOpulse Instruction for Use, provided as a separate document.

In the hospital or clinic, the study drug cartridges and devices should be stored in a secured, temperature controlled, and limited access area. At the subject's home, drug and devices should be stored in a secured area that is not close to a heat source (such as a heater, radiator, furnace, fireplace, oven, dryer, etc.). Avoid storage in unsecured, small areas (such as closets, trunks of cars, etc.).

The Sponsor or their designee reserves the right to inspect the investigational product storage area at the Investigator site before and during the study. Study drug and device will only be used solely for the purposes of this study.

12.5.2. Dispensing

Only subjects participating in the Run-in, treatment phase, and/or open-label extension of the study may receive study drug and device. Authorized, medically trained research team members will initially administer the study drug and device to randomized subjects. Each subject will be provided an INOpulse Instruction for Use describing the safe use of the iNO/INOpulse combination product.

The INOpulse settings that are used by the device to set the study drug at the appropriate dosage, i.e., the subject's sex and height should be checked and verified by research staff and entered into the IRT in order to ensure the INOpulse device is programmed correctly. The IRT will determine the dosing cohort, and will be used to program the INOpulse devices in a blinded manner.

When a subject enters the Run-in period, the subject will be given a 1 week supply of cartridges and cannulae, two INOpulse devices (a primary and a back-up device), along with any additional ancillary supplies for home use as assigned by the IRT. The subject will receive the Week 2 cartridge resupply via home delivery; to be distributed directly from the Central Distribution Center (CDC) or designee to the subject's home by a third party carrier. The subject must acknowledge receipt of the shipment, and account for each cartridge used in the IRT. At the end of the 2 week Run-in period, the subject must return to the study site with both INOpulse devices.

If the subject qualifies for enrollment in the treatment period, the subject will be given a 1 week supply of cartridges, cannulae, and two INOpulse devices (a primary and a back-up), along with any additional ancillary supplies for home use as assigned by the IRT. The subject will receive resupply shipments via home delivery; to be distributed directly from the CDC or designee to the subject's home by a third party carrier. On a monthly basis, in conjunction with resupply shipments, used study drug cartridges will be returned from the subject's home to the CDC by a third party carrier. For ALL deliveries and returns of study drug kits and device kits, acknowledgment of receipt and accountability will be completed in the IRT, documenting which kits are delivered, used, and returned from the subject's home.

If the subject enters the long term extension (Part 2), the subject will be given a 1 week supply of cartridges, cannula, and two INOpulse devices (a primary and a back-up), along with any additional ancillary supplies for home use as assigned by the IRT. The subject will receive resupply shipments via home delivery; to be distributed directly from the central distribution center or designee to the subject's home by a third party carrier. On a monthly basis, in conjunction with resupply shipments, used study drug cartridges will be returned from the subject's home to the central distribution center by a third party carrier.

Instruction regarding the direct to subject distribution and return process will be outlined in the study specific Distribution Plan.

12.5.3. Accountability of Investigational Study Products

Investigational product accountability records for the investigational products mandated by the Sponsor in accordance with all applicable regulatory requirements must be kept current and should include, but not be limited to:

- the dates, quantities, and unique identification number of investigational products received from the Sponsor
- subject identification, date, amount, and unique identification numbers dispensed
- date, amount, and unique identification numbers of investigational products returned , as appropriate

The IRT may be utilized to assist in the capture and maintenance of this information. These records must be made available for inspection by the Sponsor or their designee during the course of the study.

The Investigator or designee is responsible for the accountability of all used and unused study supplies. The Investigator or designee will maintain accurate study drug and device accountability records documenting date, quantities, and unique identification numbers of supplies received, dispensed, returned, and accounts of any study drug and device lost, missing, or damaged. The Investigator or designee will retain copies of these logs on file.

At the conclusion of the study, a final inventory of study drug will be performed by the Sponsor or their designee. Any supplies which cannot be accounted for will be documented.

Any remaining drug and devices at the end of the study will be handled as per Sponsor instructions (e.g., returned to Sponsor, CDC or their designee).

12.6. Study Drug and Device Disposition

Used and unused study drug cartridges and devices should not be destroyed or disposed of by the site, the distribution center, or by the subject. The used cartridges and devices will be returned regularly from the site, or subject home, to the CDC and/or manufacturing facility, utilizing a third party carrier.

Collection of used and unused study drug cartridges and devices will be outlined in the study specific Distribution Plan.

12.7. Treatment Usage

Treatment usage will be automatically monitored at each visit in Part 1 and Part 2, including Week 18, early termination or EOS or by site research team personnel (hours:minutes per day) by capturing the INOpulse usage log in the IRT. Additionally, the subject's INOpulse device will be shipped to the Sponsor at the EOS and/or for maintenance where the INOpulse software log can be captured in a computer database.

13. RANDOMIZATION, BREAKING OF BLINDED CODES AND INTERACTIVE RESPONSE TECHNOLOGY (IRT) SYSTEM

13.1. Randomization and Blinding

All eligible subjects will be screened for enrollment in Part 1. All eligible and consented subjects will be randomized into 1 of 2 treatment groups in a ratio of 1:1.

Randomization will be performed using an IRT system. Randomization will occur ONLY after the subject has signed the informed consent, has been enrolled into the study, and has met all Inclusion and Exclusion criteria.

Study drug should be started after randomization during the Run-in (Baseline) visit.

All study drug cartridges will be labeled with informative language that each cartridge contains up to 6.0 mg/L (4880 ppm) NO gas to allow for compliance with compressed gas transportation regulations while maintaining a blinded label. All study labels will indicate the kit number and all drug cartridges will be labeled with a blinded unique identification number prior to shipment to the investigative site or the subject's home. Drug cartridges are intended for use by a single subject who will be assigned the corresponding kit number on the study label by the IRT. Similarly, all devices will be uniquely identified, and tracked and controlled by the IRT.

13.2. Breaking of Blinded Codes

The blind may be broken only if specific urgent treatment would be dictated by knowing the treatment status of the subject.

The Investigator or designee will be able to call or login to the IRT to unblind a subject. It is **strongly recommended** to discuss the case with the Sponsor's medical monitor before unblinding.

The date, time, and reason for the unblinding must be documented in the eCRF, and the Sponsor's medical monitor must be informed as soon as possible.

13.3. Interactive Response Technology (IRT)

Selected individuals at each study center, along with subjects, will be authorized by pre-coded identification numbers to have password protected access to the designated portions of the system. Authorized individuals will interact with the IRT in accordance with the user manual. The IRT will be used by the site to assign subjects randomization numbers, dosing cohorts, and drug/device supplies.

The IRT will also be used for functions such as: accountability (by site and subjects), dispensing, reordering or replacement of INOpulse device, cartridges or ancillary supplies, programming of INOpulse devices, and emergency unblinding of subject treatment.

Corresponding messages will be sent to the study center to confirm completion of each process.

14. CONCOMITANT MEDICATIONS

Prior and concomitant medications will be coded according to the WHO Drug Dictionary and summarized by drug class and drug name for each formulation and for all subjects combined.

14.1. Allowed PAH Approved Medication Changes During the Study

Currently approved treatments include: synthetic prostacyclin (i.e., epoprostenol, a prostacyclin analog, treprostinil or iloprost), an ERA (i.e., bosentan, ambrisentan, or macitentan), and PDE-5 inhibitors (i.e., sildenafil and tadalafil).

PAH therapies may be altered or additional therapies added only for evidence of clinical worsening due to PAH as defined in the protocol throughout the trial.

LTOT flow rates should be kept constant throughout the study unless the subject has persistent desaturations to less than 88% of SpO_2, or otherwise clinically indicated. LTOT flow rate with the estimated length of use per day must be documented in the eCRF at all visits.

All PAH approved medications should be given as per standard of care, with the exception that inhaled prostaglandins (Ventavis® and Tyvaso®) and oral sildenafil doses should be not be given within 1 hour of a scheduled RHC.

15. ADVERSE EVENTS AND DEVICE DEFICIENCIES

At each study visit for Part 1 and Part 2, the Investigator will determine whether any AE has occurred. The Investigator will also instruct the subject to contact the Investigator (or designee) in between study visits to report any AEs.

Adverse events will be coded according to the current MedDRA classification in use.

The Investigator will record the nature, severity, treatment and outcome of the AE, and will determine their association to the investigational product or procedures involved in the study.

15.1. Definitions

15.1.1. Adverse Event

An AE is any untoward medical occurrence associated with the use of an investigational product in humans, whether or not considered investigational product related.

An AE can be any unfavorable or unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, without any judgment about causality. This includes any events that occur during investigational product administration or, if present prior, have worsened in severity.

The Investigator will determine and record the seriousness, severity, relationship, and outcome for all AEs.

15.1.2. Adverse Device Effect

Adverse device effect (ADE) is an AE related to the use of an investigational medical device. This includes an AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

15.1.3. Device Deficiency

Device deficiency is defined as an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse, or use error and inadequate labeling. All device deficiencies should be reported including outcome of device deficiency, regardless of whether they lead to an adverse event.

15.1.4. Suspected Adverse Reaction

A suspected adverse reaction (SAR) is an AE for which there is a reasonable possibility that the investigational product caused the AE. For the purposes of IND safety reporting, possibility means there is evidence to suggest a causal relationship between the investigational product and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by an investigational product.

15.1.4.1. Unexpected Adverse Event or Unexpected Suspected Adverse Reaction

An AE or SAR is considered unexpected if it is not listed in the adverse reactions section of the Investigator Brochure, or is not listed at the specificity or severity that has been observed.

Unexpected, as used in this definition, also refers to AEs or SARs that are mentioned in the Investigator Brochure as occurring with a class of drugs, or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned in the adverse reaction section as occurring with the particular drug under investigation.

15.1.5. Adverse Events of Special Interest

Adverse events of special interest (serious or nonserious) are those which have scientific and medical concern specific to the use of the investigational product, which may warrant ongoing monitoring and communication with Investigators in order to fully characterize and understand the events.

AESIs will be queried at each visit and documented on a separate AESI page in the eCRF and recorded on the Adverse Event eCRF page.

- Hospitalization for pulmonary reasons
- Pulmonary infections
- Important increases in chronic pulmonary medications
- Dyspnea
- Cough
- Hypoxia
- Acute respiratory failure
- Bronchitis
- Epistaxis
- Syncope, pre-syncope or loss of consciousness (new onset, or if history of syncope, recurrent syncope events)
- Clinically significant signs and/or symptoms (as determined by the Investigator) consistent with rebound PH (e.g., systemic hypotension, change in heart rate, new onset syncope, or decreased systemic oxygenation) temporally associated with acute withdrawal and including those associated with device malfunction or failure.

15.1.6. Serious Adverse Event or Serious Adverse Reaction

A SAE or SAR is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic

bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered to be a SAE.

This classification of serious events includes device deficiencies that might have led to a SAE if (a) suitable action had not been taken; or (b) intervention had not been made; or (c) circumstances had been less fortunate.

15.1.7. Unanticipated Serious Adverse Device Effect

An unanticipated serious adverse device effect (USADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. A USADE is a serious adverse device effect, which by its nature, incidence, severity or outcome has not been identified in the current version of the Investigator's Brochure.

15.1.8. Life Threatening

An AE is considered "life-threatening" if, in the view of the Investigator or Sponsor, it places the subject at immediate risk of death from the AE *as it occurred*. It does not include an AE that, had it occurred in a more severe form, might have resulted in death.

15.1.9. Serious, Unexpected, Suspected Adverse Reaction

All serious, unexpected, and suspected adverse reactions (SUSARs) must be reported by the Sponsor. Of note, in the US, the Sponsor must report an AE as a SAR only if there is evidence to suggest a causal relationship between the drug and the AE.

15.2. Severity and Causality Assessment for Adverse Events

15.2.1. Severity

Severity of an AE will be defined from the qualitative assessment of the degree of intensity of the event as determined by the Investigator or as reported by the subject. The assessment of severity is made irrespective of drug relationship or seriousness of the event and should be evaluated according to the following scales:

1 = Mild - Discomfort noticed, but no disruption to daily activity

2 = Moderate - Discomfort sufficient to reduce or affect normal daily activity

3 = Severe - Inability to work or perform normal daily activity

15.2.2. Causality Assessment for Adverse Events

The Investigator or designee is responsible for assessing the relationship between AEs and the investigational product. Additionally, the Investigator or designee is responsible for providing appropriate treatment for the event and for adequately following the event until resolution. The

clinical Investigator or responsible designee should determine the investigational product relationship using the following explanations:

Unrelated: an AE that is clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and does not meet the criteria for 'possible' or 'probable.'

Possible: the association between the AE and study treatment appears unlikely, but cannot be ruled out with certainty. An AE may be considered 'possibly related' if it meets at least 2 of the following criteria:

- It follows a reasonable temporal sequence from administration of investigational product.
- It may readily have been produced by the subject's clinical state or by environmental or toxic factors.
- It follows a known response pattern to investigational product.

Probable: an AE that is considered to be related to investigational product with a high degree of certainty. An AE may be considered probably related if it meets all of the following criteria:

- It follows a reasonable temporal sequence from administration of investigational product.
- It cannot be reasonably explained by the known characteristics of the subject's clinical state.
- It follows a known pattern of response to investigational product treatment.
- It reappears upon re-challenge.

Table 6 lists AEs that are common in this subject population, even in the absence of exposure to the study drug. The Investigator may use this as guidance while assessing the causality. If these events are deemed as an adverse drug reaction during evaluation, the Sponsor will follow the appropriate reporting procedures.

Table 6: Adverse Events Common to the PAH Population

MedDRA System Organ Class	Preferred Term
Cardiac disorders	Palpitations
	Tachycardia
	Dizziness
	Pre-syncope
	Syncope
	Oedema
	Ascites
	Chest pain
	Right ventricular heave
	Right ventricular dysfunction
	Cardiac failure
General disorders and administration site conditions	Lethargy
	Nausea
	Vomiting
Hepatobiliary disorders	Hepatomegaly
Investigations	Heart rate irregular
Metabolism and nutrition disorders	Thirst
Psychiatric disorders	Depression
Respiratory, thoracic and mediastinal disorders	Acute respiratory failure
	Bronchitis
	Dyspnoea at rest
	Dyspnoea exertional
	Dyspnoea paroxysmal nocturnal
	Cough
	Hypoxemia
	Orthopnoea
	Upper respiratory tract infection
Vascular disorders	Raynaud's phenomenon

15.3. Outcome Assessment for Adverse Events

The outcome assessment for an AE will be defined as follows:

- resolved
- resolved with sequelae
- ongoing
- death
- unknown

Pregnancy occurring in a subject is not considered an AE or SAE; however, the Investigator must collect pregnancy information for female study subjects or female partners of male study subjects if the fetus could have been exposed to the investigational device. Any pregnancy should be reported to the Sponsor using the Serious Adverse Event Report Form (SAE Report Form). Delivery details and the neonatal outcome must be recorded and reported.

15.4. Collection, Recording and Reporting of Adverse Events and Investigational Product Complaints/Deficiencies

15.4.1. Collection of Adverse Events and Serious Adverse Events

Any AE occurring prior to signing the ICF should be considered medical history or a pre-existing condition, and will be collected on the Medical History eCRF. Findings at Screening from physical exam, baseline laboratory results, etc. should also be considered medical history or pre-existing condition and be recorded accordingly.

At each visit, the Investigator will determine whether any AE has occurred and if it is related to the investigational product. Subjects will also be instructed to contact the site to report any AE that occurs between study visits. For randomized subjects, AEs and SAEs will be collected from signing of the ICF through the EOS and entered on the AE section of the eCRF.

SAEs (including those related to investigational product complaints/deficiencies) occurring from signing of the ICF through the EOS will be reported to Bellerophon Pulse Technologies Drug and Device Safety Department or their designee within 24 hours of an Investigator becoming aware of the event, using the AE/SAE page in the eCRF.

As laboratory abnormalities may fall into the category of expedited reporting, the Investigator will review the clinical laboratory test results in a timely fashion. Only those results qualifying as AEs/SAEs will be recorded in the AE section of the eCRF.

Adverse events will be coded according to the most current version of MedDRA in use. All medical device deficiencies associated with a SAE will be coded and reported as required.

For consented subjects who are screen failures prior to randomization, AEs will not be collected after the subject fails to qualify for randomization.

15.4.2. Collection of Investigational Product Complaints/Deficiencies

Information is collected on investigational product complaints/deficiencies from the Investigators. An investigation of an investigational product complaint/deficiency is performed to determine the root cause by the Sponsor. This will include evaluation of the reported complaint details, and data from the device service log when downloaded by the Sponsor. Details of collection of investigational product complaints/deficiencies will be provided to the sites in a separate site instruction. In the case of a device deficiency, the remaining investigational product study materials must be returned to the Sponsor and/or their designee for further investigation.

15.4.3. Serious Adverse Events and Medical Device Deficiency Reporting

The Sponsor shall be responsible to submit all appropriate documentation to all governing Health Authorities in accordance with local laws, regulations, and standards.

Any SAR that is both **s**erious and unexpected will be considered reportable for the investigational product and will be handled as such by the Sponsor.

The following events will be considered reportable for the investigational product and will be handled as such by the Sponsor:

1. Any associated with an SAE
2. Any investigational medical device deficiency that might have led to an SAE if:
    a. suitable action had not been taken; or
    b. intervention had not been made; or
    c. if circumstances had been less fortunate
3. New findings and/or updates in relation to already reported events
4. Any events that require remedial action

Notification of any SAE or investigational medical device deficiency, whether or not associated with the drug or device, by Investigators to the Sponsor is required **within 24 hours**. The reporting of SAEs or investigational medical device deficiencies will be conducted in accordance with ICH E2A (Clinical Safety Data Management: Definitions and Standards for expedited reporting) and local regulatory guidelines.

Any SAE must be reported on the AE/SAE eCRF in the InForm clinical database at the study site **within 24 hours** of the site staff becoming aware of the event or investigational medical device deficiency.

The initial AE/SAE eCRF entry in the InForm clinical database will include a detailed description of the event including start and stop dates, relationship, severity, and outcome assessments by the Investigator. While the AE/SAE eCRF should be completed with all necessary information including laboratory test results and diagnostic information, the information recorded on the eCRF may be supported, as appropriate, with written copies of medical records, autopsy reports, and other appropriate documents. Follow-up information (including information requested by the Sponsor) should be reported within 24 hours of availability. Any additional supporting documentation should be faxed to:

Pharmacovigilance Dept.

Fax: 1-844-332-7371

Email: btdrugsafety@bellerophon.com

If you have specific questions regarding the reporting of SAEs, you should contact the local Medical Monitor.

15.4.3.1. Site Reporting to IRB/IEC

The Investigator must also notify the local IRB/IEC which approved the study of any SAEs, AEs, or device deficiencies, in accordance with local health authority guidelines.

15.4.3.2. Sponsor Reporting to Regulatory Authorities, Investigators, and Independent Ethics Committee

The Sponsor will notify the relevant Regulatory Authorities and all participating Investigators of reports of potential safety risks from clinical studies or any other source, in accordance with applicable regulations. Upon notification of an event, the Sponsor will determine the need for reporting and the timeline for reporting in each active country. The reporting of SAEs will be conducted in accordance with ICH E2A (Clinical Safety Data Management: Definitions and Standards for expedited reporting) and local regulatory guidelines.

Upon request, the Sponsor shall report the results of device deficiency evaluations to Regulatory Authorities and participating Investigators. Where applicable, Investigators will submit this information to their local IRB/IEC.

All AEs, SAEs, and device deficiencies will be reported to the regulatory authorities and IECs in accordance with the current country specific regulatory and IRB/IEC requirements. These will be outlined in the Safety Management Plan for this study.

15.5. Steering Committee

This study will be designed and conducted under the direction of a Steering Committee (SC) made up of clinicians experienced in pulmonary and cardiovascular research, who will be responsible for the protocol and data collection tool, oversight of study execution, review, and publication of the data. The SC will also review and screen requests for access to the data for the purpose of secondary publications. The members will be global.

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A SC charter will be developed with input from the SC and the Sponsor.

15.6. Data Monitoring Committee

The members of the Data Monitoring Committee (DMC) will be experienced clinicians in the care of PAH subjects and experienced in the conduct of trials in PAH. A DMC will review data at predefined times as described in the DMC charter and make decisions regarding early termination of the study, as well as dosing cohort decisions. In order to protect the safety of subjects in this study, the DMC will alert the Sponsor if there is any safety concern based on the accumulated data. The DMC will also advise on the appropriateness of continuing the study due

to any safety concern. All SAEs will be sent to the DMC in a timely manner for review. Protocol violations will be reviewed on a quarterly basis (or more frequently if needed) per site.

A DMC charter will be developed with input from the DMC committee members, the SC and the Sponsor.

15.7. Independent Clinical Events Committee

The members of the ICEC will be experienced clinicians in the care of PAH subjects and experienced in adjudication for clinical trials in PAH. The ICEC will review and adjudicate the following:

- All SAEs
- Rebound PH
- Subject eligibility when eligibility may be unclear

An independent research organization experienced in the adjudication of cardiovascular events will supervise the collection of data on all events. They will maintain a website where the committee members can access the data, determine the need for more data, and record their findings. The research organization will coordinate all ICEC meetings and be responsible for transferring the adjudication data to the Sponsor.

The data presented to the ICEC members will be reviewed and any information that may lead to un-blinding of the reviewer will be removed.

The Sponsor, appointed research organization, and ICEC will create a pre-determined SMQ list to capture all potential event terms that may be reported and attributed to PAH. Once all parties come to agreement on the list, the electronic adjudication system (EAS) will be programmed to identity potential events for adjudication based on the SMQ list. All AEs will be imported into the EAS and compared against the SMQ programmatically. Events will be managed on a daily basis by adjudication staff. Adjudication staff will collect essential elements for review by the ICEC.

An ICEC charter will be developed with input from the ICEC members, the steering committee, research organization and the Sponsor.

16. STATISTICAL CONSIDERATIONS

This section provides a general description of the statistical methods to be used in analyzing both safety and efficacy data. The key statistical issues or considerations will be addressed. A more detailed statistical analysis plan will be provided in a separate document that will be finalized before unblinding of treatment assignment.

Unless otherwise specified, all statistical tests will be one-sided with a significance level of 0.025. Summary statistics will be provided for all study variables with descriptive statistics (number of observations, mean, standard deviation, median, minimum, and maximum) for numerical (or continuous) variables and with frequency and percentage for categorical variables.

All statistical analysis will be conducted using SAS version 9.2 or higher (SAS Institute Inc., Cary, NC).

16.1. Population(s) for Analysis

An intent-to-treat (ITT) population that consists of all randomized subjects who remained eligible after the Run-in period will be used for all the efficacy analyses: subjects will be analyzed in the treatment group to which they were randomized

A safety population that includes all randomized subjects who receive the study treatment and who remained eligible after the Run-in period will be used for all the safety analyses. In addition, an analysis of safety for all randomized subjects who receive the study treatment and who became ineligible after the Run-in period will be conducted. For the safety population, subjects will be summarized according to the treatment they received during the study.

16.2. Sample Size Determination

Interim Analysis will be conducted by an independent DMC after 18-week 6MWD data are available from 75 patients. The purpose of the interim analysis is to stop the trial for an early efficacy or futility conclusion or to continue the trial to 150 or 188 - patients (total randomized is higher to account for an anticipated 20% dropout rate). Group sequential early stopping criteria and sample size re-estimation methodology are further described in the statistics section of this protocol. They are constructed to control overall type 1 error at 0.025, 1-sided. Simulations assuming true underlying mean treatment difference in 6MWD ranging from 30-70 meters and standard deviations from 50 to 75 meters yielded >87% power for all cases except the most extreme case (mean difference 30 meters and SD 75), for which power was ~71%.

Subjects who do not comply with the required device adherence, as well as who do not meet the study entry criteria at Week 2, will be withdrawn from the study.

16.3. Efficacy Analyses

16.3.1. Primary Efficacy Endpoint

The primary endpoint is to evaluate the efficacy of iNO as measured by the placebo-adjusted change in 6-minute walk distance (6MWD) from baseline to 18 weeks. The average of the two 6MWDs at Week 2 (after run-in) will be used as the baseline value for analysis of data. The

6MWD at Week 2 should be obtained on all subjects, even if the subject does not qualify to enter into the treatment phase.

The primary statistical test for the primary endpoint will be performed using a repeated measures mixed model with the baseline stratification factor (i.e., the prostanoid usage status), - treatment arm, week, and treatment-by-week interaction as the main effects. As a covariate, baseline 6MWD assessment will be included in the model. In case the normality assumption is substantially violated (i.e., graphical assessment of residuals from the analysis model and the Shapiro-Wilk test statistic graphical assessment of the residuals from the analysis model and), the primary efficacy endpoint will be analyzed using the van Elteren test stratified by the prostanoid usage status. Least Squares mean differences, standard errors, 95% confidence intervals will be derived from the analysis model.

Exploratory analyses will be performed to evaluate the effects of demographics and baseline characteristics on the efficacy response with appropriate statistical methods. Subgroup analyses based on study drug usage, background therapies, demographics and baseline characteristics, as well as other study compliance status will be conducted. Additional statistical methods such as mixed effects model and Cochran–Mantel–Haenszel (CMH) test (for dichotomized response analysis) may be utilized in the exploratory analyses.

16.3.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

1. TTCW*: The time (in days) from start of treatment to first event (first day the event is noted), with iNO as compared to placebo, measured from baseline to week 18. TTCW event is defined as any of the following:
    a. Death (all-cause mortality)
    b. Atrial septostomy
    c. Hospitalization due to worsening of PAH (adjudicated)
    d. Start of new specific PAH treatment (endothelin receptor antagonists [ERAs], phosphodiesterase type-5 [PDE-5] inhibitors or prostanoids), an increase in the dose of an ERA or PDE-5, increase in the dose or frequency of an inhaled prostanoids, or an increase in the dose of an intravenous or subcutaneous prostanoids by >10%.
    e. Decrease of >15% from baseline or > 30% compared with the last study related measurement in 6MWD and should be confirmed by a repeat measurement performed at least 14 days later
    f. Worsening of WHO Functional Class (e.g., from Class II to Class III or IV, OR Class III to Class IV); and should be confirmed by a repeat assessment at least 14 days later
2. Change in WHO Functional Class, with iNO as compared to placebo, from baseline to 18 weeks.

The TTCW endpoint will be analyzed with log-rank test stratified by the prostanoid usage status. The censoring time points for the analyses include the time points at which subjects drop out of the study or complete the study without any of the specified events.

The WHO Functional Class endpoint will be analyzed with the same method as that for the primary endpoint. Change from baseline to week 18 will also be evaluated as an exploratory analysis.

16.3.3. Tertiary Endpoints

1. Change in health-related quality of life (using SF-36 version 2 health survey), with iNO as compared to placebo, from baseline to 18 weeks
2. Change in pulmonary hemodynamics (i.e., cardiac output [CO], cardiac index [CI], mean pulmonary artery pressure [mPAP], mean pulmonary capillary wedge pressure [mPCWP], systolic pulmonary artery pressure [sPAP], diastolic pulmonary artery pressure [dPAP], pulmonary vascular resistance [PVR], and oxygen saturation by pulse oximeter [SpO_2], mixed venous O_2, and right atrial pressure [RAP]) measured by right heart catheterization (RHC), with iNO as compared to placebo, from baseline to 18 weeks, in a subset of subjects (approximately 50), at selected sites
3. Change in echocardiogram measurements right ventricular function (including right ventricular fractional area change, systolic pulmonary artery pressure [sPAP], tricuspid annular motion/tricuspid annular plane systolic excursion, tricuspid annular systolic velocity, and Tei index) and left ventricular function (including left ventricular ejection fraction [LVEF], LV size, and improvement in LV early diastolic relaxation velocity), with iNO as compared to placebo, from baseline to 18 weeks, in a subset of subjects (approximately 50), at selected sites
4. Change in NT-proBNP, with iNO as compared to placebo, from Screening to 18 weeks
5. Change in Borg dyspnea score immediately following 6MWT, with iNO as compared to placebo, from baseline to 18 weeks
6. Change in 6MWD as related to degree of drug adherence, with iNO as compared to placebo, from baseline to 18 weeks
7. The number of subjects with unsatisfactory clinical response, with iNO as compared to placebo, from baseline to 18 weeks. Defined as: WHO Functional Class III or IV symptoms with no improvement in 6MWD
8. Number of subjects undergoing heart-lung or lung transplantation, number of subjects listed for transplantation, and deaths while awaiting transplantation, from baseline to 18 weeks
9. Medical resource utilization, with iNO as compared to placebo, from baseline from baseline to 18 weeks

For continuous (or numerical) response endpoints, the statistical analyses will be performed using the same method as that for the primary efficacy endpoint. Binary (or dichotomized) response endpoints will analyzed by CMH test stratified by the prostanoid usage status.

16.3.4. Multiplicity Adjustment

To control the Type-1 error rate at a level of 0.025 1-sided, a hierarchal gate keeping procedure will be applied to test the significant difference between the treatment groups in the primary and secondary endpoints in the following order:

1. 6MWD
2. TTCW
3. WHO Functional Class

Each test will be evaluated at the appropriate p-value alpha spending function. The procedure will stop if lack of significance is found for any of the variables and the remaining test(s) in the sequence (as mentioned above) will also be concluded as non-significant.

16.3.5. Handling Missing Data

Missing data imputation for primary endpoint:

For primary analysis, i.e. change from baseline at Week 18, missing data will not be imputed.

The following missing data imputation techniques will be employed for sensitivity analyses of primary endpoint.

1) Last Observation Carry Forward (LOCF) approach will be applied for subjects not withdrawing trial due to adverse events, for subjects withdrawing trial due to adverse events (including deaths), worst value (for e.g. zero for 6MWD) will be assigned at EOS visit.
2) Worst-case imputation approach I (i.e. impute the missing value for a subject with worst value (within the subject) for all subjects who withdraw prematurely for any reason. The value of zero for 6MWD will be imputed for all deaths.
3) Worst-case imputation approach II (i.e., impute the missing value for a subject in the active and Placebo dose group by the worst result of all subjects with non-missing assessments in their respective assigned dose groups). The value of zero for 6MWD will be imputed for all deaths.
4) Worst-case imputation approach III (i.e. impute the missing value for a subject in the active dose group by the worst result of all subjects with non-missing assessments in the same active dose groups and impute the missing value for a subject in placebo group by his/her last available assessment prior to the missing assessment. The value of zero for 6MWD will be imputed for all deaths.

Missing data imputation for secondary endpoint:

For all the other efficacy endpoints, the last observation carry forward (LOCF) approach will be used in handling the missing data as that used in the EARLY study (Galiè 2008).

16.4. Safety Analyses

Adverse events will be coded using the MedDRA dictionary. AEs (events that are new in onset or aggravated in severity following treatment) will be summarized under each dosing cohort, by

system organ class (SOC) and preferred term (PT). Comparisons between dosing cohorts will be made using Fisher's exact test for the proportion of subjects with a particular AE (grouped under one preferred term). Serious AEs (including death) will be summarized. In addition, AEs will be summarized by severity and relation to study drug.

Adverse events of special interest (AESI) include:

- Respiratory related AEs
- Epistaxis
- Syncope (new onset, or if history of syncope, recurrent syncope events)
- Clinically significant signs and/or symptoms (as determined by the Investigator) consistent with rebound PH (e.g., systemic hypotension, change in heart rate, new onset syncope, or decreased systemic oxygenation) temporally associated with acute withdrawal and including those associated with device malfunction or failure.

Other safety evaluations include:

1. Incidence of device malfunction and/or device failure leading to an AE
2. Incidence of rebound PH
3. Clinically significant changes in the following:
    a. Clinical laboratory tests
    b. Pulmonary function tests
    c. Vital signs

All safety data will be summarized by treatment groups with descriptive statistics or frequency table.

16.5. Interim Analysis

A formal interim analysis is planned in this study as follows:

1. Stop for futility (null hypothesis is accepted; there is no difference between iNO and Placebo).
2. Stop for efficacy (null hypothesis is rejected; there is difference between iNO and Placebo favoring iNO).
3. Sample size determination (decision to use blinded or unblinded data).
4. Stop in case of safety concerns. Safety concerns may be some imbalances in adverse events frequency which is not in favor of iNO. No formal statistical guideline is provided for this purpose, the sponsor relies on the medical expertise of DMC members.
5. Continue the trial with the planned sample size until next stage if point 1, 2 or 4 not apply.

The following two designs will define the interim analysis strategy:

1) Design 1: Groups Sequential Design (for efficacy part)
2) Design 2: Sample Size Re-estimation (SSR) (for futility and sample size re-estimation)

The interim analysis schedule planned as follows:

Schedule	Requirement
1st	After 75 patients complete 18 Weeks of blinded treatment phase.
Final	After 150/188 (depending on CP and PP) patients complete 18 Weeks of blinded treatment phase.

Traditional group sequential design (GSD) alpha spending function Gamma=-3 (Hwang, Shih, deCani, 1990) is used to control the overall type 1 error at 0.025, 1-sided. The interim analysis rule (Table 7) is as follows.

Table 7: Interim and Final Analysis Rules

Category	Rule
Efficacy	At first interim analysis (after 75 patients), if the one-sided p<0.0046 then the study will stop for efficacy (Wald Statistics)
Efficacy	At final analysis (after 150 patients or 188 patients depending on CP and PP), if the one-sided p < 0.0229 then the study will yield an efficacy conclusion. (based on CHW Statistics)
Futility	If conditional power (CP) or predictive power (PP) ≤ 10% then the study stops for futility.
Continue	If 10% < CP and PP < 30% then trial continues to 150 patients.
SSR	If 30% ≤ CP or PP < 80% then the sample size required to boost the CP or PP to 80% is computed. If this sample size exceeds 188 (upper limit) then the study continues at N = 150 else to 188.
Continue	If CP and PP ≥ 80% then the trial continues to N = 150 patients

This is the "promising zone" sample size re-estimation (SSR) design of Mehta & Pocock (2011), which uses the Cui, Hung, Wang (1999) method of analysis to combine the test statistics for the separate analyses of the IA and post-IA parts of the trial, if the trial does not stop at IA.

The final analysis is via weighted Z statistic using equal weights for the IA and post IA test statistics. It requires p<0.0229 1-sided for statistical significance to control the overall type 1 error level at 0.025 1-sided per the gamma=-3 error spending function (Hwang, Shih, deCani 1990).

17. MONITORING PROCEDURES

17.1. Study Monitoring

The study will be periodically monitored and/or audited by a representative of Bellerophon Pulse Technologies LLC. It is the responsibility of the Principal Investigator or responsible designee to provide all study records, including, but not limited to, case report forms and source documentation, to the monitor and/or auditor at their visit.

Regulatory Agencies, in the person of a scientifically trained and properly authorized employee of the Agency, may request access to all study records, including source documents, for inspection and copying.

The site's Institutional Review Board/Independent Ethics Committee (IRB/IEC) may also review their individual site's study records, including, but not limited to, case report forms and source documentation at any time.

18. RESPONSIBILITIES

18.1. Quality Control and Quality Assurance

Prior to study initiation, there will be an Investigator meeting and/or individual site initiation visits to prepare Investigators and study staff, and to standardize performance at each study center associated with the study. Data will be collected by the study site coordinator and/or designee as specified on the site's "Signature Sheet and Delegation of Responsibility Log" and verified at the site by the clinical research associate (CRA). These data will be monitored and verified to the original medical records. Data will be entered by trained and qualified study site personnel into a validated EDC system managed by the Sponsor. Changes to the data will be made by the research team at the site according to ICH GCP styles of recording data and will be documented via an audit trail.

18.2. Audits and Inspections

To ensure compliance with GCP and all applicable regulatory requirements, Bellerophon Pulse Technologies LLC may conduct a quality assurance audit. Regulatory agencies and other governing bodies may also conduct a regulatory inspection of this study.

To ensure compliance with the protocol, GCPs, and all applicable regulatory requirements, Bellerophon Pulse Technologies LLC or an independent third party on behalf of the Sponsor, may conduct a quality assurance audit. Regulatory agencies or the local health authority may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the Investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and/or any relevant issues. The Investigator will be informed of such audit(s).

18.3. Investigator and Study Staff Requirements

All Investigators must be qualified by training and experience to conduct the proposed research, and must accept responsibility for all research activities at their site.

Prior to study initiation, the Investigator will complete and submit to the Sponsor all documents required by 21 CFR Part 50, 56, and 312, ISO 14155, and/or ICH (E6) (Section 8.0), including financial disclosure information as required. Additionally, each Investigator must assure the study staff is qualified by training and experienced to assist with the proposed research. This training must be documented and maintained at the study site.

Upon completion or termination of the study, the Investigator will submit a final written report to the IRB/IEC. The Investigator will provide the Sponsor or designee with copies of all IRB/IEC actions regarding the study.

19. DATA MANAGEMENT AND RECORDKEEPING

19.1. Electronic Case Report Forms

Electronic case report forms are created using a validated EDC system. They are to be completed in English for all subjects. Table 8 below lists the roles and access levels for this study.

Table 8: Roles and Access Levels to Remote Data Capture System

Role/Privilege	Data Manager	CRA	Site Coordinator	Investigator	Reviewer
Browse	Y	Y	Y	Y	Y
Update Data	N	N	Y	N/Y[a]	N
Update Discrepancy	Y	Y	Y	Y	N
Verify	N	Y	N	N	N
Approve	N	N	N	Y	N

[a] Data update privileges may be granted upon specific request following completion of the required training.

Entered data will be reviewed manually and electronically for consistency and correctness with the protocol. All discrepancies will be forwarded to appropriate EDC users for resolution. An electronic audit trail will be maintained to track all changes to the database.

Refer to study specific eCRF completion guidelines for further details.

19.2. Case Report Forms

Electronic Case Report Forms are to be completed for all consented subjects. For subjects who sign the ICF but are subsequent screen failures, no AE or SAE data will be collected after these subjects fail to meet eligibility criteria and do not to qualify for randomization.

All eCRF will be completed in a timely fashion, preferably within 5 days after the subject visits, which will enable timely monitoring visits.

19.3. External Data

Any data that is collected electronically will be uploaded from the vendor's database to Bellerophon Pulse Technologies database via secure transfer. Details of this process will be coordinated with the vendor and described in a Data Transfer Specifications document. Laboratory data that is collected locally by the site will be entered directly in the eCRF.

19.4. Inspection of Records

In compliance with local regulations, US Federal regulations and ICH GCP guidelines, it is required that the Investigator and institution permit authorized representatives of the Sponsor, of the regulatory agency(s), and the IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform the subject and obtain their consent to permit

named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

19.5. Retention of Records/Critical Documents

In compliance with ICH GCPs and applicable regulatory requirements, copies of all records (e.g., informed consent documents, laboratory data slips, source documents, safety reports, test article dispensing records) which support the eCRFs, must be retained in the files of the responsible Investigator for a minimum of 2 years (for EU: records to be retained for 15 years) following notification by Sponsor that all investigations at all sites are completed, terminated, or discontinued. If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the trial records, custody must be transferred to a person who will accept the responsibility. Bellerophon Pulse Technologies LLC must be notified in writing of the name and address of the new custodian.

20. ETHICS

The study will be conducted in accordance with this protocol, the principles that have their origins in the Declaration of Helsinki, as well as ICH GCP and applicable federal, state, and local regulatory requirements. All essential documents will be archived.

The protocols and local ICFs must be reviewed and approved by each of the participating institutions' IRB/IEC prior to the initiation of subject recruitment. The IRB/IEC must be notified of all subsequent protocol amendments. In addition, progress reports will be submitted to the IRB/IEC by the Investigator as indicated by IRB/IEC's guidelines. Each IRB/IEC must meet the FDA's, and/or European Medicines Agency (EMA), International Conference on Harmonization (ICH), and any additional state and/or national requirements for composition, documentation, and operational procedures.

The Investigator shall provide the Sponsor with the IRB/IEC's written notification of approval along with the IRB/IEC membership list and/or statement that the IRB/IEC operates in accordance with GCP.

20.1. Informed Consent Form(s) for Study Subjects

The informed consent must contain all elements required by the FDA under 21 CFR Part 50 and ICH (E6) (Section 4.8), as well as any other elements required by state, local and institutional policies and applicable ISO standards. All subjects (or legally authorized representative) must provide consent in writing after having had adequate time to ask questions and consider their participation in the study. Consent must be obtained before any protocol related procedures that are not part of the subject's normal care. Written documentation of consent must be provided by signing a Bellerophon Pulse Technologies approved informed consent document. The date and time the consent was finalized should be recorded in the subject's medical chart. The subject or their legal representative must receive a copy of a dated, and signed consent form according to ICH GCP guidelines. The exact definition of legal representative should be determined for a hospital by its IRB/IEC in compliance with local and state statutes. Subjects will be informed of any significant new finding developed during the course of the research that may affect their decision to continue participation.

Failure to provide written informed consent renders the subject ineligible for the study.

20.2. Independent Ethics Committee/Institutional Review Board

20.2.1. Amendments to the Protocol

Neither the Investigator nor the Sponsor will amend nor modify the protocol without written notification of the other. All amendments must be approved by the Sponsor prior to implementation. All amendments must be submitted to the IRB/IEC as required. The IRB/IEC must approve major amendments prior to implementation at the study site except in the case of ensuring subject safety, as required.

21. REPORTS AND PUBLICATIONS

The Sponsor recognizes that the institution and/or Principal Investigator may desire to publish or present information related to the subject matter of the study. No such publication or presentation, including without limitation, any such publication or presentation by an individual Principal Investigator in a multicenter study, may occur without the express written approval of the Sponsor which approval shall not be unreasonably withheld.

In the case of a multicenter study, no individual publication shall be made until after the planned multi-center publication, or 12 months after study completion, whichever shall first occur.

In the event the Institution and/or Principal Investigator desire to make a publication or presentation, the Institution and/or Principal Investigator will provide a copy of the proposed publication or presentation of the study to the Sponsor 45 days prior to submission for publication or presentation in order to ascertain whether public disclosure will adversely affect patent rights, copyrights, or proprietary rights or any other interest of the Sponsor. In the event of objection by the Sponsor, for any reason, the institution and Principal Investigator further agree to delay the publication or presentation until modifications or revisions to the publication or presentation have been made which are mutually satisfactory to the Institution/Principal Investigator and the Sponsor.

This trial will be listed on clinicaltrials.gov.

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APPENDIX A. INSTRUCTIONS FOR 6MWT. SIX MINUTE WALK TEST AND OXIMETRY (OXYGEN SATURATION, SPO_2)

A standardized Six-Minute Walk Test (6MWT) will be performed in accordance with the guidelines of the (American Thoracic Society 2002). The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The turnaround points should be marked (e.g. with a cone).

The distance walked in six minutes (6MWD) will be calculated and recorded. If the patient discontinues the test prematurely, the time (mm:ss) and distance walked will be recorded.

Requirement of rescue medication including requirement of oxygen therapy and any adverse events occurring during the 6MWT will be recorded.

Oxygen therapy, oxygen should be given at their standard rate. Oxygen should be provided through an oxygen cylinder on a wheeled cart connected to the INOpulse device. The INOpulse device should be attached to the oxygen cylinder.

During the study the 6MWT should be done about the same time of day to avoid diurnal variation.

REQUIRED EQUIPMENT

1) Countdown timer (or stopwatch)
2) Mechanical lap counter
3) Two small cones to mark the turnaround points
4) A chair that can be easily moved along the walking course
5) Worksheets on a clipboard
6) Oxygen tank and INOpulse device
7) Sphygmomanometer
8) Portable pulse oximeter

PATIENT PREPARATION

1) Comfortable clothing should be worn.
2) Appropriate shoes for walking should be worn.
3) Subjects should use their usual walking aids during the test (cane, walker, etc.).
4) The subjects's usual medical regimen should be continued.
5) A light meal is acceptable before early morning or early afternoon tests.
6) Subjects should not have exercised vigorously within 2 hours of beginning the test.

MEASUREMENTS

1) Repeat testing should be performed about the same time of day to minimize intraday variability.
2) A "warm-up" period before the test should not be performed.
3) The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Compete portion of CRF.

4) Measure and record baseline heart rate and oxygen saturation (SpO_2) and follow manufacturer's instructions to maximize the signal and to minimize motion artifact. Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable.

Instruct the patient as follows:

"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

Start now, or whenever you are ready."

1) Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.
2) Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

After the first minute, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go."

When the timer shows 4 minutes remaining, tell the patient the following: "Keep up the good work. You have 4 minutes to go."

When the timer shows 3 minutes remaining, tell the patient the following: "You are doing well. You are halfway done."

When the timer shows 2 minutes remaining, tell the patient the following: "Keep up the good work. You have only 2 minutes left."

When the timer shows only 1 minute remaining, tell the patient: "You are doing well. You have only 1 minute to go."

Do not use other words of encouragement (or body language to speed up).

If the patient stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair

over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

When the timer is 15 seconds from completion, say this: "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."

When the timer rings (or buzzes), say this: "Stop!" Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

1) Record the end of walk Borg dyspnea level
2) Measure SpO_2 and pulse rate from the oximeter and then remove the sensor.
3) Record the number of laps from the counter
4) Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.
5) Congratulate the patient on good effort and offer a drink of water.

References:

(American Thoracic Society, 2002)