INHALED NITRIC OXIDE/INOPULSE DEVICE COMBINATION PRODUCT

PULSE-CVD19-001

A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF PULSED, INHALED NITRIC OXIDE (iNO) VERSUS PLACEBO IN SUBJECTS WITH MILD OR MODERATE CORONAVIRUS DISEASE (COVID-19)

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1. STUDY CONTACT INFORMATION

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INVESTIGATOR'S AGREEMENT AND SPONSOR'S SIGNATURE PAGE

I have read the attached protocol PULSE-CVD19-001: A RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF PULSED, INHALED NITRIC OXIDE (iNO) VERSUS PLACEBO IN SUBJECTS WITH MILD OR MODERATE CORONAVIRUS DISEASE (COVID-19), 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.

Wassim Fares 08/19/2020

Wassim Fares, MD MSc Date
Chief Medical Officer
Bellerophon Pulse Technologies LLC

Fernande 19 August 2020

Peter Fernandes, M. Pharm Date
Chief Regulatory, Safety & Quality Officer
Bellerophon Pulse Technologies LLC

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 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, STUDY TO ASSESS THE EFFICACY AND SAFETY OF PULSED, INHALED NITRIC OXIDE (iNO) VERSUS PLACEBO IN SUBJECTS WITH MILD OR MODERATE CORONAVIRUS DISEASE (COVID-19)

Study center(s): Multiple center study enrolling approximately 500 subjects.

Principal Investigator: TBD

Study period:

First subject enrolled (planned): 2Q2020

Study completion: After the last subject completes 30 day follow up of the last iNOpulse dose

Duration of treatment:

Subjects will receive placebo or iNO125 mcg/kg IBW/hr for 24 hours daily until resolution of hypoxemia, protocol defined respiratory failure, hospital discharge or Day 28, whichever occurs first. In instances where continuous INOpulse dosing is not feasible (eg, due to PPE limitations), INOpulse should be used a minimum of 12 hours daily.

Study Objectives:

Primary Objective: The primary objective in this study is to verify the efficacy of iNOpulse in subjects with COVID-19.

Secondary Objective: The secondary objective in this study is to evaluate the safety of iNOpulse in subjects with COVID-19.

Endpoints:

Primary Endpoint: Proportion of subjects who died or had respiratory failure through Day 28.

Respiratory failure is defined as one of:

- Endotracheal intubation and mechanical ventilation
- Extracorporeal membrane oxygenation
- High-flow nasal cannula oxygen delivery (i.e., reinforced nasal cannula delivering heated, humidified oxygen with fraction of delivered oxygen ≥0.5 and flow rates of ≥30 l/min)
- Noninvasive positive pressure ventilation
- Clinical diagnosis of respiratory failure with initiation of none of the above listed measures only when clinical decision-making is driven solely by resource limitation or in the event the subject is not intubated due to do not intubate (DNI) or do not resuscitate (DNR) status

Secondary Endpoints:

1. 8-point NIAID ordinal scale (**Table 1**) assessed at Days 7, 14, 28 and day of discharge
2. Proportion of subjects to recover, defined as return to room air or baseline oxygen requirements, or discharged alive from hospital [Through Day 28]
3. Proportion of subjects discharged alive from hospital [Through Day 28]

4. Duration of hospitalization [Through Day 28]
5. Mortality [Through Day 28]
    - All-cause mortality
    - Cardiopulmonary mortality
6. Proportion of subjects with a negative conversion of RT-PCR from a nasopharyngeal or bilateral nasal swab [Through Day 28]

Safety Endpoint:

- Proportion of subjects with adverse events leading to study drug discontinuation [Through Day 28]

Table 1: 8-point NIAID Ordinal Scale

Score	Outcome
1	Death
2	Hospitalized, requiring mechanical ventilation or ECMO
3	Hospitalized, requiring non-invasive ventilation or high flow oxygen
4	Hospitalized, requiring supplemental oxygen
5	Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)
6	Hospitalized, not requiring supplemental oxygen - not requiring ongoing medical care (COVID-19 related or otherwise)
7	Not hospitalized - limitation on activities and/or requiring home oxygen
8	Not hospitalized, no limitations on activities

Methodology:

No targeted therapeutic treatments for coronavirus (COVID-19) have been identified. Symptoms range from mild upper respiratory tract infection to severe pneumonia and death. Progression of end stage disease is unpredictable with high fatality rates in mechanically ventilated subjects as a result of multi-organ failure. Prevention of COVID-19 progression in spontaneously breathing subjects with mild to moderate disease may result in improved morbidity and mortality as well as limiting the burden to limited healthcare resources.

Inhaled nitric oxide (iNO) is a well-established safe and effective vasodilator and has been approved for the treatment of persistent pulmonary hypertension in neonates. Bellerophon is currently developing INOpulse for the treatment of chronic pulmonary hypertension (WHO Group 1, 3 and 5) with ongoing Phase 2 and Phase 3 studies in PH-ILD, PH-COPD and PH-SARC. The proprietary INOpulse® technology, utilizes high concentration pulses to ensure a precise and constant dose regardless of a subject's respiratory rate or inspiratory volume. The pulsatile technology allows dose titration, providing much higher doses/concentrations than currently available in hospital based systems, as well as reduces the overall size of the therapy, allowing it to be administered at home. Also as a result of the pulsatile technology, iNO is delivered during the first half of each inspiration and therefore, does not increase the risk of exposure to aerosolized virus during INOpulse administration.

The pathobiology of COVID-19 infection may provide a rationale for the mechanism of the severe hypoxemia. The virus enters the pneumocyte via the ACE2 receptor resulting in inflammation and causing lung injury. As the virus gains access to the systemic circulation it can enter the endothelial

cells where the ACE2 receptor is widely expressed on the cell surface resulting in an endotheliitis and which can potentially involve multiple organs (Varga, 2020). This inflammatory process, causing endothelial dysfunction, shifts the endothelium toward a more vasoconstrictive, procoagulant state. This endothelial dysfunction could potentially lead to pulmonary vasoconstriction with resultant ventilation perfusion (V/Q) mismatch in the lung. Inhaled nitric oxide (iNO) has the potential to optimize V/Q matching by dilating the blood vessels in the least affected areas of the lung. In addition, nitric oxide has an important role in the immune response and has been demonstrated to inhibit the replication of SARS-CoV (Akerstrom, 2005; Keyaerts, 2004) with evidence also supporting a clinical benefit in subjects with SARS (Chen, 2004). SARS-CoV-2, the pathogen responsible for COVID-19, shares 79.5% of its genomic sequence with SARS-CoV (Guo, 2020). It is therefore postulated that iNO might have dual beneficial effects in COVID-19 subjects.

The clinical spectrum of the COVID-19 infection ranges from mild signs of upper respiratory tract infection to severe pneumonia and death. Currently, the probability of progression to end stage disease is not well understood, however, preventing progression in subjects with mild or moderate disease would improve morbidity/mortality and reduce the impact on limited healthcare resources. Furthermore, reducing the need for positive pressure ventilator support as observed in the Chen study (2004) may limit lung damage. Based on the genomic similarities between the two coronaviruses, the data in SARS-CoV supports the potential for iNO to provide benefit for subjects infected with COVID-19. Exogenous iNO in subjects who have mild to moderate COVID-19 could prevent further deterioration and potentially improve the time to recovery.

INOpulse therapy using iNO125 (125 mcg/kg IBW/hr) was authorized for treatment of COVID-19 via FDA's Intermediate Expanded Access Program in March 2020. Eligible patients were COVID-19 positive by RT-PCR, or with high suspicion of infection, and receiving supplemental oxygen at no more than 10 L/min. Data from the first 25 patients treated with INOpulse for COVID-19 was conducted in April 2020, and demonstrated INOpulse was well tolerated with no increase in methemoglobin levels above 1.5%. Of the 22 COVID-19 positive patients to complete treatment with INOpulse, 19 completed treatment without deterioration (86%) with 3 showing signs of deterioration (1 death and 2 intubated). The median time for INOpulse treatment was 4 days and the median time from start of INOpulse treatment to hospital discharge was 6 days.

This is a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of pulsed iNO compared to placebo in subjects with COVID-19 who are hospitalized and require supplemental oxygen without assisted ventilation. Subjects will be randomized to receive placebo or iNO125 mcg/kg IBW/hr 24 hours daily until resolution of hypoxemia, protocol defined respiratory failure, hospital discharge or Day 28, whichever occurs first. In instances where continuous INOpulse dosing is not feasible (eg, due to PPE limitations), INOpulse should be used a minimum of 12 hours daily. Subjects will be followed through 30 days after discontinuation of INOpulse therapy to assess their clinical status.

Randomization will be stratified for use of Remdesivir for the treatment of COVID-19. In addition randomization will be stratified by: oxygen flow rate, NT-proBNP and comorbidities (diabetes, hypertension, cardiovascular disease [including ischemic heart disease, heart failure, cerebrovascular disease, peripheral vascular disease] and obesity [BMI $\geq$30]). COVID-19 treatment should not be changed during INOpulse therapy. Changes to COVID-19 SOC treatments occurring during the conduct of the trial will be accounted for in stratification criteria as appropriate, and will be managed accordingly in the statistical analysis.

Prior to receiving treatment with INOpulse, subjects will be screened to confirm eligibility. All subjects (ie, both active and placebo) should be offered current standard of care for treatment of COVID-19.

COVID-19 infection must be confirmed via positive RT-PCR, or have high index of suspicion of infection with results pending. Upon successful completion of screening, subjects will receive treatment with placebo or iNO 125 mcg/kg IBW/hr up until resolution of hypoxemia, protocol defined respiratory failure, hospital discharge or Day 28, whichever occurs first. In instances where continuous INOpulse dosing is not feasible (eg, due to PPE limitations), INOpulse should be used a minimum of 12 hours daily.

Prior to randomization, the following screening assessments (0 to -14 days prior to randomization) will be completed as described in **Table 2**:

- Informed consent
- COVID-19 RT-PCR obtained from an upper respiratory tract specimen within the previous 4 days. Subjects may be positive for COVID-19 or have high suspicion of infection at the time of randomization with RT-PCR results pending. If a subject is randomized based upon a high suspicion of COVID-19 infection and the swab RT-PCR comes back negative, a repeat RT-PCR swab can be taken and the subject can be continued on INOpulse pending the repeat results. If the repeat RT-PCR results come back negative, the subject should be discontinued from INOpulse therapy. If the subject deteriorates after discontinuation of INOpulse, the Investigator should consider the reintroduction of INOpulse therapy.
- CT scan or chest x-ray after onset of symptoms and within 14 days of randomization
- CBC with differential, chemistry panel (sodium, potassium, chloride, CO2, BUN, creatinine, glucose), LFTs (AST/ALT and total bilirubin), triglycerides, troponin (High Sensitivity Cardiac Troponin [HS-cTN]*)*, procalcitonin, ferritin, fibrinogen, D-dimer NT-proBNP and LDH. If available locally, CRP, Von Willebrands Factor, Factor VIII Activity, Protein C, Protein S, Homocysteine, Antithrombin 3, Thrombelastography (TEG), G6PD deficiency and Prothrombin gene G2021A. Lab results obtained within the previous 48 hours are acceptable for screening purposes if there has not been a significant change in the subject's clinical status.
- Pregnancy test (urine or serum) for women of child-bearing potential
- Vital signs (heart rate, respiratory rate, blood pressure, temperature)
- Oxygen saturations
- Document oxygen flow requirements
- Medical History including a documented reason for hospital admission
- Physical exam
- Review inclusion and exclusion eligibility criteria
- Review of prior and concomitant medications, that includes all current COVID-19 treatments (all therapies prescribed for the treatment of COVID-19)

On the day of Randomization (Day 0):

- Review inclusion and exclusion eligibility criteria
- Review of prior and concomitant medications, that includes all current COVID-19 treatments (all therapies prescribed for the treatment of COVID-19)
- Electrocardiogram (ECG)
- Vital signs (heart rate, respiratory rate, blood pressure, temperature)
- Oxygen saturations
- Document oxygen flow requirements

- Upon initiating INOpulse, methemoglobin should be < 3% and SpO2 > 89% (with supplemental oxygen if required) prior to continuing with treatment. Methemoglobin will be monitored prior, during the 1st hour (every ½ hour), and approximately 4-5 hours after initiation of INOpulse therapy.
- Adverse event(s) assessment

Daily assessments while on INOpulse and hospitalized (up to Day 27) will be performed as follows:

- Review of prior and concomitant medications, that includes all current COVID-19 treatments (all therapies prescribed for the treatment of COVID-19)
- Oxygen flow requirements
- While hospitalized and on INOpulse, vital signs (heart rate, respiratory rate, blood pressure, temperature), SpO2 via pulse oximetry and methemoglobin will be measured **twice daily** to minimize exposure to healthcare professionals
    - In the event an increase in oxygen flow rate is clinically indicated, vital signs and SpO2 should be monitored every 6 hours until stabilized.
- Adverse event(s) assessment
- Respiratory Failure status
- Clinical status using an 8-point NIAID ordinal scale (**Table 1**)

At **End of Treatment** (INOpulse discontinuation), the following assessments will be completed:

- CBC with differential, chemistry panel (sodium, potassium, chloride, CO2, BUN, creatinine, glucose), LFTs (AST/ALT and total bilirubin), triglycerides, troponin (High Sensitivity Cardiac Troponin [HS-cTN], procalcitonin, ferritin, fibrinogen, D-dimer, NT-proBNP and LDH. If available locally, CRP, Von Willebrands Factor, Factor VIII Activity, Protein C, Protein S, Homocysteine, Antithrombin 3, Thrombelastography (TEG), G6PD deficiency and Prothrombin gene G2021A
- COVID-19 RT-PCR obtained by nasopharyngeal or bilateral nasal swab
- Review of prior and concomitant medications, that includes all current COVID-19 treatments (all therapies prescribed for the treatment of COVID-19)
- Electrocardiogram (ECG)
- Vital signs, methemoglobin and oxygen saturations
- Oxygen flow requirements
- Respiratory Failure Status
- Clinical status using an 8-point NIAID ordinal scale (**Table 1**)
- Upon discontinuation of INOpulse, irrespective of reason, subjects should be monitored for 1 hour for symptoms of pulmonary rebound which include hypoxemia, bradycardia, tachycardia, systemic hypotension, shortness of breath, near-syncope, and syncope. SpO2, BP and vital signs should be measured every 30 minutes for 1 hour.
- Adverse event(s) assessment
- Download usage data from the INOpulse device

If a subject has completed **End of Treatment** (off INOpulse) and is **still hospitalized** (not discharged), **daily** assessments (up to Day 28 or day of discharge if earlier) will be performed as follows:

- Respiratory Failure status
- Clinical status using an 8-point NIAID ordinal scale (**Table 1**)
- Adverse event(s) assessment
- Concomitant medications

At time of hospital **discharge,** if before the End of Study assessment, the following assessments will be completed:

- CT scan or chest x-ray prior to discharge, as clinically indicated
- Duration of hospitalization
- Respiratory Failure Status
- Clinical status using an 8-point NIAID ordinal scale (**Table 1)**
- Adverse event(s) assessment
- Concomitant medications

If a subject has been discharged from the hospital, the following assessments will be completed on **Day 7, Day 14 and Day 28** via telephone:

- Respiratory Failure status
- Clinical status using an 8-point NIAID ordinal scale (**Table 1**)
- Adverse event(s) assessment
- Concomitant medications

End of Study: Thirty (30) days following the **last dose** of INOpulse, subjects will be assessed for the following via telephone (or in person in the unlikely event the subject is still hospitalized):

- Respiratory Failure status
- Clinical status using an 8-point NIAID ordinal scale (**Table 1**)
- Adverse event(s) assessment
- Concomitant medications

At **Early Discontinuation** (if applicable), the following assessments will be completed:

- CT scan or chest x-ray any time prior to discharge, as clinically indicated
- CBC with differential, chemistry panel (sodium, potassium, chloride, CO2, BUN, creatinine, glucose), LFTs (AST/ALT and total bilirubin), triglycerides, troponin (High Sensitivity Cardiac Troponin [HS-cTN], procalcitonin, ferritin, fibrinogen, D-dimer, NT-proBNP and LDH. If available locally, CRP, Von Willebrands Factor, Factor VIII Activity, Protein C, Protein S, Homocysteine, Antithrombin 3, Thrombelastography (TEG), G6PD deficiency and Prothrombin gene G2021A
- COVID-19 RT-PCR obtained by nasopharyngeal or bilateral nasal swab
- Review of prior and concomitant medications, that includes all current COVID-19 treatments (all therapies prescribed for the treatment of COVID-19)

- Electrocardiogram (ECG)
- Vital signs, methemoglobin and oxygen saturations
- Oxygen flow requirements
- Respiratory Failure Status
- Clinical status using an 8-point NIAID ordinal scale (**Table 1**)
- Upon discontinuation of INOpulse, irrespective of reason, subjects should be monitored for 1 hour for symptoms of pulmonary rebound which include hypoxemia, bradycardia, tachycardia, systemic hypotension, shortness of breath, near-syncope, and syncope. SpO2, BP and vital signs should be measured every 30 minutes for 1 hour.
- Adverse event(s) assessment
- Download usage data from the INOpulse device

If at any time, patient care decisions are made based upon resource limitations (eg, availability of PPE), the decision, date and reason should be documented.

Criteria for Study Drug Interruption: If methemoglobin >7%, SpO2 falls below 80%, or clinically significant INOpulse-related adverse events are observed, INOpulse therapy should be interrupted. INOpulse therapy may be re-started at the discretion of the Investigator.

Criteria for Study Drug Discontinuation: If methemoglobin > 7% is sustained or severe respiratory failure, multi-organ failure and/or other conditions arise that impair the ability of the subject to receive INOpulse, INOpulse therapy should be permanently discontinued. Severe respiratory failure does not include subjects who require use of High Flow Nasal Cannula (HFNC) ≤ 15 L/minute (these subjects can continue to receive INOpulse treatment).

In order to minimize the loss of data, it is critical all subjects are followed for 30 days post cessation of INOpulse therapy unless consent is withdrawn or a subject is lost to follow up.

Number of subjects and sites:

Multi-center study enrolling approximately 500 subjects at approximately 30 sites.

Diagnosis and main criteria for inclusion and exclusion:

Inclusion criteria:

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

1. Signed Informed Consent Form (and assent as appropriate) prior to the initiation of any study mandated procedures or assessments.
2. At least 18 years old
3. [REMOVED IN AMENDMENT #1]
4. Subject must be hospitalized and have the following:
   - proven or high suspicion of SARS-CoV-2 infection, and

- requiring oxygen supplementation defined as:
    - SpO2 ≤ 92% regardless of supplemental oxygen (ie, on room air or on oxygen); or
    - SpO2 ≥ 92% on supplemental O2 and in the opinion of the Investigator it is not safe to decrease or remove the supplemental oxygen
- require supplemental oxygen of no more than 10 L/minute, and
- radiologic suspicion or proof of COVID-19 pneumonitis (chest x-ray or CT scan)

5. 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.
6. Willing and able to comply with treatment schedule and study procedures.

Exclusion criteria:

Subjects who meet any of the following criteria are not eligible for enrollment:

1. Participating in any other clinical trial of an investigational treatment for COVID-19
2. Methemoglobin > 3%
3. Evidence of severe acute multi organ failure as defined as (any one of the following):

Organ System	**Severe Criteria**
Hepatic	Jaundice with bilirubin 8-10 mg/DL
Renal	Dialysis or Renal Replacement Therapy
Hematologic	DIC
Cardiovascular	Systemic hypotension not responsive to vasopressors
CNS	Coma

4. Use of assisted ventilation prior to initiation of INOpulse such as:
    - Any system of Non Invasive Ventilation (NIV), with Positive End-Expiratory Pressure (PEEP) (eg, high flow nasal cannula, CPAP [unless used for OSA], or BiPAP) or mechanical ventilation
5. Pregnancy, or positive pregnancy test in a pre-dose examination
6. Open tracheostomy
7. Clinical contra-indication, as deemed by the Investigator
8. Chronic use of a nitric oxide donor agent such as nitroglycerin or drugs known to increase methemoglobin such as lidocaine, prilocaine, benzocaine, nitroprusside, isosorbide, or dapsone at screening
9. Known history or clinical evidence of systolic heart failure, left ventricular dysfunction (LVEF < 40 %)

10. Subjects reporting massive hemoptysis associated with the current illness or with radiologically proven pulmonary embolus

Investigational product, dosage and mode of administration:

Subjects will be randomized to receive placebo, or iNO125 mcg/kg IBW/hr (approximately equivalent to 20 ppm) 24 hours daily until resolution of hypoxemia, protocol defined respiratory failure, hospital discharge or Day 28, whichever occurs first. In instances where continuous INOpulse dosing is not feasible (eg, due to PPE limitations), INOpulse should be used a minimum of 12 hours daily.

Subjects will be treated by means of an INOpulse device using an INOpulse 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).

Matching placebo will be supplied in size 0.074 liter aluminum cartridge containing N2, 99.999% gas, identical to that of the active drug cartridge (iNO 125) to ensure double-blind is maintained.

The study subject's characteristics that are used by the INOpulse device to administer the study drug at the appropriate dosage, i.e., the subject's sex and height, will be assessed during screening and verified by research staff in order to confirm the INOpulse device is programmed correctly.

INOpulse cannot be used concurrently with PAP or PEEP.

INOpulse cartridges will be labelled for the PULSE-CVD19-001 program. All cartridges will meet the requirements for this clinical trial.

The investigational study drug, iNO, will be manufactured by Mallinckrodt Pharmaceuticals located in Port Allen, Louisiana USA.

Reference INOpulse Instructions for Use.

Statistical methods:

Primary Efficacy Analysis:

The primary analysis will be analyzed using a logistic regression model (Agresti, 2007, John Wiley and Sons) with treatment, age, gender and baseline stratification factors (used for stratified randomization) as covariates. Supportive analysis may be carried out while including other baseline subject level and site level covariates as needed (to be specified in the SAP).

The primary analysis is conducted at Day 28, however, we plan to conduct sensitivity analyses at Day 7 and Day 14 and day of discharge.

In addition, where appropriate, we plan to conduct time to event analysis to supplement the proportional analyses.

Details around the analysis plan will be provided in the SAP.

Expected Sample-Size

Initial assessment of the sample size is based on the historical experience of ~30% of hospitalized COVID-19 subjects deteriorating to needing increased respiratory support and the experience in our Emergency Expanded Access that indicates ~15% deteriorate.

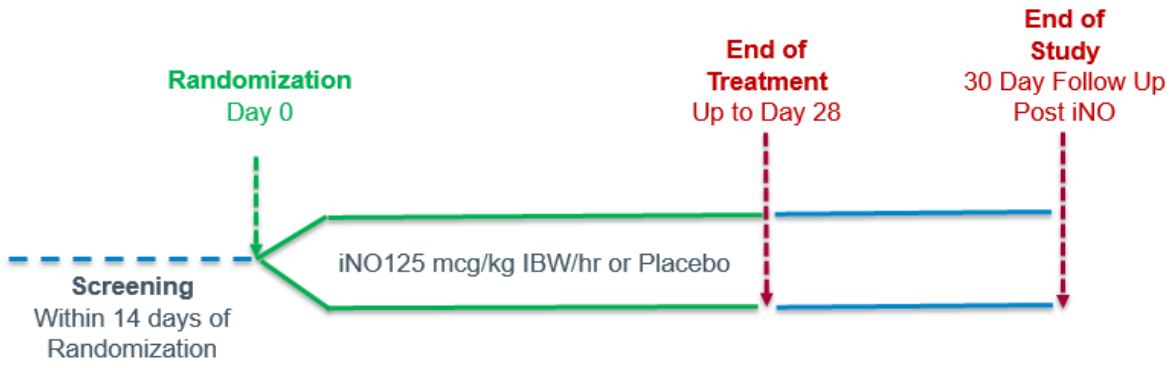
Using 30% for the placebo arm and 15% for the iNO arm results in a sample size of 382 for a 1:1 randomized trial with 90% power for one-sided p-value of 0.025.

Based on this analysis, we are targeting a sample size of ~500 subjects. However, we note that the sample size may need to be re-assessed as the data on COVID-19 are rapidly evolving.

Interim Analysis:

An interim analysis for futility is planned after ~100 subjects have completed assessments through Day 28 in order to assess the failure rate in the iNO group versus placebo for the primary endpoint (death and respiratory failure). The interim analysis will be carried out by an independent external DMC based on pre specified criteria and stopping rules as detailed in the SAP.

Study Diagram:



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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
AE	adverse event
ACE	Angiotensin-converting enzyme
BP	blood pressure
CDC	Central Distribution Center
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
Co-V	Coronavirus
CPAP	continuous positive airway pressure
CRF	case report form
CT	computed tomography
DBP	diastolic blood pressure
DIC	disseminated intravascular coagulation
DMC	Data Monitoring Committee
DNI	Do Not Intubate
DNR	Do Not Resuscitate
GCP	Good Clinical Practice
HR	heart rate
IBW	ideal body weight
ICF	informed consent form
ICH	International Conference of Harmonization
IEC	International Electrotechnical Commission
iNO	inhaled nitric oxide
ILD	Interstitial Lung Disease
IL-6	Interleukin - 6
IRB	Institutional Review Board
LVEF	left ventricular ejection fraction

Abbreviation or Specialist Term	Explanation
MEDDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
N2	nitrogen
NO	nitric oxide
NIAID	National Institute of Allergy and Infectious Diseases
(NIV)	Non Invasive Ventilation
O2	oxygen
OSA	obstructive sleep apnea
PEEP	Positive End-Expiratory Pressure
PPE	personal protective equipment
ppm	parts per million
PH	pulmonary hypertension
RR	respiratory rate
RT-PCR	Reverse transcription polymerase chain reaction
SAE	serious adverse event
SpO2	oxygen saturation by pulse oximeter
SAR	serious adverse reaction
SARC	Sarcoidosis
SARS	Serious Acute Respiratory Syndrome
SUSAR	Suspected Unexpected Serious Adverse Reactions
USADE	Unanticipated Serious Adverse Device Effect
V/Q	Ventilation Perfusion

5. INTRODUCTION

No targeted therapeutic treatments for coronavirus (COVID-19) have been identified. Symptoms range from mild upper respiratory tract infection to severe pneumonia and death. Progression of end stage disease is unpredictable with high fatality rates in mechanically ventilated subjects as a result of multi-organ failure. Prevention of COVID-19 progression in spontaneously breathing subjects with mild to moderate disease may result in improved morbidity and mortality as well as limiting the burden to limited healthcare resources.

Inhaled nitric oxide (iNO) is a well-established safe and effective vasodilator and has been approved for the treatment of persistent pulmonary hypertension in neonates. Bellerophon is currently developing INOpulse for the treatment of chronic pulmonary hypertension (WHO Group 1, 3 and 5) with ongoing Phase 2 and Phase 3 studies in PH-ILD, PH-COPD and PH-SARC. The proprietary INOpulse® technology, utilizes high concentration pulses to ensure a precise and constant dose regardless of a subject's respiratory rate or inspiratory volume. The pulsatile technology allows dose titration, providing much higher doses/concentrations than currently available in hospital based systems, as well as reduces the overall size of the therapy, allowing it to be administered at home. Also as a result of the pulsatile technology, iNO is delivered during the first half of each inspiration and therefore, does not increase the risk of exposure to aerosolized virus during iNO administration.

The pathobiology of COVID-19 infection may provide a rationale for the mechanism of the severe hypoxemia. The virus enters the pneumocyte via the ACE2 receptor resulting in inflammation and causing lung injury. As the virus gains access to the systemic circulation it can enter the endothelial cells where the ACE2 receptor is widely expressed on the cell surface resulting in an endotheliitis and which can potentially involve multiple organs (Varga, 2020). This inflammatory process, causing endothelial dysfunction, shifts the endothelium toward a more vasoconstrictive, procoagulant state. This endothelial dysfunction could potentially lead to pulmonary vasoconstriction with resultant ventilation perfusion (V/Q) mismatch in the lung. Inhaled nitric oxide (iNO) has the potential to optimize V/Q matching by dilating the blood vessels in the least affected areas of the lung. In addition, nitric oxide has an important role in the immune response and has been demonstrated to inhibit the replication of SARS-CoV (Akerstrom, 2005; Keyaerts, 2004) with evidence also supporting a clinical benefit in subjects with SARS (Akerstrom, 2005; Chen, 2004). SARS-CoV-2, the pathogen responsible for COVID-19, shares 79.5% of its genomic sequence with SARS-CoV (Guo, 2020). It is therefore postulated that iNO might have dual beneficial effects in COVID-19 subjects.

The clinical spectrum of the COVID-19 infection ranges from mild signs of upper respiratory tract infection to severe pneumonia and death. Currently, the probability of progression to end stage disease is not well understood, however, preventing progression in subjects with mild or moderate disease would improve morbidity/mortality and reduce the impact on limited healthcare resources. Furthermore, reducing the need for positive pressure ventilator support as observed in the Chen study (2004) may limit lung damage. Based on the genomic similarities between the two coronaviruses, the data in SARS-CoV supports the potential for iNO to provide benefit for subjects infected with COVID-19. Exogenous iNO in subjects who have mild to moderate COVID-19 could prevent further deterioration and potentially improve the time to recovery.

INOpulse therapy using iNO125 (125 mcg/kg IBW/hr) was authorized for treatment of COVID-19 via FDA's Intermediate Expanded Access Program in March 2020. Eligible patients were COVID-19 positive by RT-PCR, or with high suspicion of infection, and receiving supplemental oxygen at no more than 10 L/min. Data from the first 25 patients treated with INOpulse for COVID-19 was conducted in April 2020, and demonstrated INOpulse was well tolerated with no increase in methemoglobin levels above 1.5%. Of the 22 COVID-19 positive patients to complete treatment with INOpulse, 19 completed treatment without deterioration (86%) with 3 showing signs of deterioration (1 death and 2 intubated). The median time for INOpulse treatment was 4 days and the median time from start of INOpulse treatment to hospital discharge was 6 days.

6. OBJECTIVES

6.1 Primary Objective

The primary objective in this study is to verify the efficacy of INOpulse in subjects with COVID-19.

6.2 Secondary Objective:

The secondary objective in this study is to evaluate the safety of INOpulse in subjects with COVID-19.

7. ENDPOINTS

7.1. Primary Endpoint

Proportion of subjects who died or had respiratory failure through Day 28.

Respiratory failure is defined as one of:

- Endotracheal intubation and mechanical ventilation
- Extracorporeal membrane oxygenation
- High-flow nasal cannula oxygen delivery (i.e., reinforced nasal cannula delivering heated, humidified oxygen with fraction of delivered oxygen ≥0.5 and flow rates of ≥30 l/min)
- Noninvasive positive pressure ventilation
- Clinical diagnosis of respiratory failure with initiation of none of these measures only when clinical decision-making is driven solely by resource limitation or in the event the subject is not intubated due to (DNI) or do not resuscitate (DNR) status

7.2. Secondary Endpoints

1. 8-point NIAID ordinal scale assessed at Day 7, 14, 28 and day of discharge (Table 1)
2. Proportion of subjects to recover, defined as return to room air or baseline oxygen requirements, or discharged alive from hospital [Through Day 28]
3. Proportion of subjects discharged alive from hospital [Through Day 28]
4. Duration of hospitalization [Through Day 28]
5. Mortality [Through Day 28]
   - All-cause mortality
   - Cardiopulmonary mortality
6. Proportion of subjects with a negative conversion of RT-PCR from a nasopharyngeal or bilateral nasal swab [Through Day 28]

7.3. Safety Endpoint

Proportion of subjects with adverse events leading to study drug discontinuation [Through Day 28]

7.4. Overall Study Design

This is a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of pulsed iNO compared to placebo in subjects with COVID-19 who are hospitalized and require supplemental oxygen without assisted ventilation. Prior to receiving treatment with INOpulse, subjects will be screened to confirm eligibility. All subjects (ie, both active and placebo) should be offered current standard of care for treatment of COVID-19. COVID-19 infection must be confirmed via positive RT-PCR, or have high index of suspicion of infection with results pending. Upon successful completion of screening, subjects will be randomized to receive placebo or iNO125 mcg/kg IBW/hr 24 hours daily until resolution of hypoxemia, protocol

defined respiratory failure, hospital discharge or Day 28, whichever occurs first. In instances where continuous INOpulse dosing is not feasible (eg, due to PPE limitations), INOpulse should be used a minimum of 12 hours daily. Subjects will be followed through 30 days after discontinuation of INOpulse therapy to assess their clinical status.

7.5. Treatment Assignment

Subjects will be randomized and stratified for the use of Remdesivir for the treatment of COVID-19. In addition randomization will be stratified by: oxygen flow rate, NT-proBNP and comorbidities (diabetes, hypertension, cardiovascular disease [including ischemic heart disease, heart failure, cerebrovascular disease, peripheral vascular disease] and obesity [BMI ≥30]).

8. STUDY POPULATION

8.1. Number of Subjects to be Studied

Approximately 500 subjects will be randomized.

8.2. Inclusion Criteria

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

1. Signed Informed Consent Form (and assent as appropriate) prior to the initiation of any study mandated procedures or assessments.
2. At least 18 years old
3. [REMOVED IN AMENDMENT #1]
4. Subject must be hospitalized and have the following:
   - proven or high suspicion of SARS-CoV-2 infection, and
   - requiring oxygen supplementation defined as:
     - SpO2 ≤ 92% regardless of supplemental oxygen (ie on room air or on oxygen); or
     - SpO2 ≥ 92% on supplemental O2 and in the opinion of the Investigator it is not safe to decrease or remove the supplemental oxygen
   - require supplemental oxygen of no more than 10 L/minute, and
   - radiologic suspicion or proof of COVID-19 pneumonitis (chest x-ray or CT scan)
5. 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.
6. Willing and able to comply with treatment schedule and study procedures.

8.3. Exclusion Criteria

Subjects who meet any of the following criteria are not eligible for enrollment:

1. Participating in any other clinical trial of an investigational treatment for COVID-19
2. Methemoglobin > 3%
3. Evidence of severe multi organ failure as defined as (any one of the following):

Organ System	**Severe Criteria**
Hepatic	Jaundice with bilirubin 8-10 mg/DL
Renal	Dialysis or Renal Replacement Therapy
Hematologic	DIC

Organ System	Severe Criteria
Cardiovascular	Systemic hypotensive state not responsive to vasopressors
CNS	Coma

4. Use of assisted ventilation prior to initiation of INOpulse such as:
    - Any system of Non Invasive Ventilation (NIV), with Positive End-Expiratory Pressure (PEEP) (eg, high flow nasal cannula, CPAP [unless used for OSA] or, BiPAP) or mechanical ventilation
5. Pregnancy, or positive pregnancy test in a pre-dose examination
6. Open tracheostomy
7. Clinical contra-indication, as deemed by the Investigator
8. Chronic use of a nitric oxide donor agent such as nitroglycerin or drugs known to increase methemoglobin such as lidocaine, prilocaine, benzocaine nitroprusside, isosorbide or dapsone at screening
9. Known history or clinical evidence of systolic heart failure, left ventricular dysfunction (LVEF < 40 %)
10. Subjects reporting massive hemoptysis associated with the current illness or with radiologically proven pulmonary embolus

9. SUBJECT DISCONTINUATION, WITHDRAWAL AND TERMINATION FROM THE STUDY

9.1. Subject Discontinuation from Study Drug/Device

Vital status (whether alive or dead) will be determined on all subjects who prematurely discontinue. The specific reason for discontinuation will be documented. 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 defined as clinically significant cardiopulmonary instability such as systemic arterial oxygen desaturation, hypoxemia, bradycardia, tachycardia, systemic hypotension, shortness of breath, near-syncope, and syncope occurring after acute withdrawal of study drug.
5. If methemoglobin > 7% is sustained or severe respiratory failure, multi-organ failure and/or other conditions arise that impair the ability of the subject to receive INOpulse, INOpulse therapy should be permanently discontinued.

9.2. Subject Withdrawal from Study

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.

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.

In order to minimize the loss of data, it is critical all subjects are followed for 30 days post cessation of INOpulse therapy unless consent is withdrawn or a subject is lost to follow up.

If at any time, patient care decisions are made based upon resource limitations (eg, availability of PPE), the decision, date and reason should be documented.

9.3. 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.

9.4. 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))and in accordance with FDA Guidelines on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency.

10. TABLE 2: SCHEDULE OF ASSESSMENTS

Assessments	Screening	Baseline/ Randomization	On INOpulse (Up to Day 28) (Hospitalized)		Off INOpulse (Hospitalized)	Hospital Discharge* (if prior to End of Study)	If Discharged (Phone Call)	End of Study**	Early Discontinuation***
	0 to -14 days prior to Baseline	Day 0	Daily (Up to Day 27)	End of Treatment	Daily (Up to Day 28 or Day of Discharge if Earlier)	Day of Discharge	Day 7 Day 14 Day 28 (± 2 days)	30 Day Follow Up Post INOpulse completion (± 3 days)	If Applicable
Informed consent	X								
Medical History[10]	X								
Review Eligibility Criteria	X	X							
Prior & Concomitant Medications[9]	X	X	X	X	X	X	X	X	X
RT-PCR for COVID-19[1]	X			X					X
Chest CT Scan or x-ray[4]	X					X			X
Pregnancy Test (urine or serum)	X								
Vital signs[2]	X	X	X	X					X
Methemoglobin[3]		X	X	X					X
SpO_2 via pulse oximetry[7] & O2 flow rate	X	X	X	X					X
Electrocardiogram (ECG)		X		X					X

Assessments	Screening	Baseline/ Randomization	On INOpulse (Up to Day 28) (Hospitalized)		Off INOpulse (Hospitalized)	Hospital Discharge* (if prior to End of Study)	If Discharged (Phone Call)	End of Study**	Early Discontinuation***
	0 to -14 days prior to Baseline	Day 0	Daily (Up to Day 27)	End of Treatment	Daily (Up to Day 28 or Day of Discharge if Earlier)	Day of Discharge	Day 7 Day 14 Day 28 (± 2 days)	30 Day Follow Up Post INOpulse completion (± 3 days)	If Applicable
Lab Evaluation[6]	X			X					X
Physical Examination	X								
Clinical status using 8-point NIAID ordinal scale			X	X	X	X	X	X	X
Respiratory Failure Status				X	X	X	X	X	X
Monitor for pulmonary rebound for 1 hr post INOpulse discontinuation[8]				X (upon INOpulse discontinuation)					X
INOpulse Device Set up & Dose Programming[5]		X							
Drug Dispensing[5]		X	X						
Download of INOpulse usage data				X					X
AE and SAE		X	X	X	X	X	X	X	X

[1] RT-PCR test for COVID-19 obtained from an upper respiratory tract specimen is required within 4 days of randomization. Another sample should be obtained from the nasopharynx or bilateral nares using a swab at End of Treatment. Subjects may be positive for COVID-19 or have high suspicion of infection at the time of randomization with RT-PCR results pending. If a subject is randomized based upon a high suspicion of COVID-19 infection and the swab RT-PCR comes back negative, a repeat RT-PCR swab can be taken and the

subject can be continued on INOpulse pending the repeat results. If the repeat RT-PCR results come back negative, the subject should be discontinued from INOpulse therapy. If the subject deteriorates after discontinuation of INOpulse, the Investigator should consider the reintroduction of INOpulse therapy

[2]Vital signs measured twice daily from Baseline until the last dose of INOpulse. Vital signs include heart rate, respiratory rate, blood pressure, and temperature. In the event an increase in O2 flow rate is clinically indicated, SpO2 should be monitored every 6 hours until stabilized. Document oxygen flow requirements.

[3] Methemoglobin assessed via Masimo RAD-57 (provided by Sponsor). Methemoglobin should be < 3% and SpO2 >89% (with supplemental O2 required) prior to continuing with treatment and should be monitored prior to, during the 1st hour (every ½ hour) and approximately 4-5 hours after initiation of INOpulse therapy. Thereafter, methemoglobin should be assessed twice daily (in conjunction with study drug cartridge changes) and remain ≤ 7 %. Otherwise, study drug should be discontinued.

[4] Chest x-ray or CT scan following onset of symptoms within 14 days prior to randomization and any time prior to discharge, as clinically indicated.

[5] Subjects will receive iNO125 mcg/kg IBW/hr or placebo for 24 hrs daily (until resolution of hypoxemia, protocol defined respiratory failure, discharge or Day 28 whichever occurs first.. In instances where continuous INOpulse dosing is not feasible (eg, due to PPE limitations), INOpulse should be used a minimum of 12 hours daily.

[6] Local lab tests to be done prior to start of study drug and at End of Treatment. Labs include CBC w/differential, chemistry panel (sodium, potassium, chloride, CO2, BUN, creatinine, glucose), LFTs (AST/ALT and total bilirubin), troponin (High Sensitivity Cardiac Troponin [HS-cTN]), D-dimer, NT-pro-BNP (if NT-pro-BNP is not available locally, BNP can be drawn and converted using the online calculator: https://www.cardio.med.tohoku.ac.jp/calc/nt-probnp.html), LDH, fibrinogen, ferritin, triglycerides, pro-calcitonin. If available at the local lab, also include CRP, Von Willebrands Factor, Factor VIII Activity, Protein C, Protein S, Homocysteine, Antithrombin 3, Thrombelastography (TEG), G6PD deficiency and Prothrombin gene G2021A. Lab results obtained within the previous 48 hours of randomization are acceptable for screening purposes if there has not been a significant change in the subject's clinical status.

[7] Upon initiation of treatment, SpO2 should be monitored to ensure levels are >89%. During INOpulse therapy, SpO2 should be monitored twice daily to ensure levels are > 80%. In the event an increase in O2 flow rate is clinically indicated, SpO2 should be monitored every 6 hours until stabilized. Oxygen flow requirements should be documented throughout the study.

[8] Symptoms of pulmonary rebound include hypoxemia, bradycardia, tachycardia, systemic hypotension, shortness of breath, near-syncope and syncope. If signs or symptoms of rebound are observed, the INOpulse should be restarted and the Investigator should contact the Sponsor. SpO2, BP and vital signs should be measured every 30 minutes for 1 hour.

[9] All prior and concomitant medications, including all over-the-counter medications and all current COVID-19 treatments (all therapies prescribed for the treatment of COVID-19

[10] Medical history to include the reason for hospital admission.

*Complete Hospital Discharge Assessments only if it occurs before the End of Study. Otherwise, if the subject is still in hospital at the time of End of Study (30 day follow up post INOpulse completion), complete only the End of Study assessments indicated.

**Subjects will be assessed via telephone if discharged from the hospital. The assessments are to be performed in person, in the unlikely event the subject is still hospitalized.

***Early Discontinuation if methemoglobin > 7% is sustained or severe respiratory failure, multi-organ failure and/or other conditions arise that impair the ability of the subject to receive INOpulse, INOpulse therapy should be permanently discontinued. Severe respiratory failure does not include subjects that require use of High Flow Nasal Cannula ≤ 15L/minute (these subjects can continue to receive INOpulse treatment). It is critical early discontinuation subjects are followed for 30 days following last INOpulse therapy. This does not include if subjects withdraws consent or is lost to follow up.

10.1. Details of Study Assessments

Timing of all study assessments is detailed in the Schedule of Study Assessments in **Table 2**.

10.1.1. Informed Consent

At Screening, each subject must provide informed consent in writing after having had adequate time to ask questions and consider his/her participation in both parts of this study. Consent must be obtained prior to any protocol related procedure or assessment that is not part of the subject's normal care. 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.

10.1.2. Medical History

At Screening, relevant medical history and demographics (sex, race, and ethnicity) will be assessed. Medical history is to include the reason for hospital admission.

10.1.3. Prior and Concomitant Medications

All prior and concomitant medications, including all over-the-counter medications and all current COVID-19 treatments (all therapies prescribed for the treatment of COVID-19), will be recorded.

10.1.4. Physical Examination

A physical examination of the following body systems should be performed. Height and sex will be recorded during screening to calculate ideal body weight as used to program INOpulse dose. It is recommended the following body systems are reviewed:

- Head and neck
- Skin
- Eyes, Ears, Nose &Throat
- Respiratory
- Cardiovascular
- Musculoskeletal
- Abdomen
- Neurological
- Genitourinary
- Lymphatic
- Extremities
- Other

10.1.5. Chest Imaging

A chest CT scan or x-ray performed following the onset of symptoms and within 14 days prior to randomization. If clinically indicated per the Investigator, another chest CT scan or x-ray will be performed any time prior to discharge.

10.1.6. RT-PCR COVID-19 Test

Confirmation of viral infection will be performed using COVID-19 RT-PCR from an upper respiratory tract specimen within 4 day of randomization. If the initial COVID-19 RT-PCR swab is negative and there is still a high suspicion of COVID-19 infection, a repeat swab sample can be taken for RT-PCR testing. Another sample should be obtained from the nasopharynx or bilateral nares using a swab at End of Treatment (Up to Day 28).

10.1.7. Vital Sign Measurements

Vital sign measurements will include heart rate (HR), respiratory rate (RR), blood pressure (BP, systolic and diastolic), and temperature. Oxygen flow rate and any changes to flow rate will be documented. SpO2 will also be documented and monitored to ensure levels remain >80% during the study and >89% upon initiation of treatment on Day 0.

10.1.8. Respiratory Failure Status

Respiratory failure is defined as one of:

- Endotracheal intubation and mechanical ventilation
- Extracorporeal membrane oxygenation
- High-flow nasal cannula oxygen delivery (i.e., reinforced nasal cannula delivering heated, humidified oxygen with fraction of delivered oxygen ≥0.5 and flow rates of ≥30 l/min)
- Noninvasive positive pressure ventilation
- Clinical diagnosis of respiratory failure with initiation of none of these measures only when clinical decision-making is driven solely by resource limitation or in the event the subject is not intubated due to do not intubate (DNI) or do not resuscitate (DNR) status

10.1.9. 12-Lead Electrocardiogram (ECG)

12-Lead ECGs will be obtained and read locally after the subject has rested in a supine position for at least 5 minutes. Date, time, heart rate, and ECG interpretation will be recorded.

10.1.10. 8-point NIAID Ordinal Scale

The ordinal scale is an assessment of the subject's clinical status. The subject's clinical status should be assessed as described in **Table 2** and documented in medical records. Assessments should be performed every morning when subjects are hospitalized and via phone if discharged from the hospital as detailed in **Table 2**.

The 8-point NIAID Ordinal Scale is provided on the following page.

The scale is as follows:

Score	Outcome
1	Death
2	Hospitalized, requiring mechanical ventilation or ECMO
3	Hospitalized, requiring non-invasive ventilation or high flow oxygen
4	Hospitalized, requiring supplemental oxygen
5	Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)
6	Hospitalized, not requiring supplemental oxygen - not requiring ongoing medical care (COVID-19 related or otherwise)
7	Not hospitalized - limitation on activities and/or requiring home oxygen
8	Not hospitalized, no limitations on activities

10.1.11. Pregnancy Test

Females of childbearing potential must have a negative serum or urine pregnancy test as described in **Table 2**. All female subjects should take adequate precaution to avoid pregnancy by using two highly effective birth control methods for the duration of the study, which includes:

- 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
- diaphragm
- condom with spermicide

Sexually active males at risk of causing a pregnancy must ensure their female partner(s) are using two methods of birth control (as described above) for the duration of the study.

10.1.12. Methemoglobin

Methemoglobin will be assessed prior to initiating INOpulse, during the 1St hour (every ½ hour) of the first dose of INOpulse and approximately 4-5 hours after initiating INOpulse therapy. Methemoglobin should be < 3% and SpO2 >89% (with supplemental O2 required) prior to continuing with treatment.

Following initiation of treatment, methemoglobin will be assessed twice daily while on INOpulse. Levels should not exceed >7%, otherwise the study drug should be interrupted and/or discontinued.

Sponsor will provide Masimo RAD-57 with rainbow probe to monitor methemoglobin in subjects treated with INOpulse.

Criteria for Study Drug Interruption: If methemoglobin exceeds 7%, SpO2 falls below 80%, or clinically significant iNO-related adverse events are observed, INOpulse therapy should be interrupted. INOpulse therapy may be re-started at the discretion of the Investigator.

Criteria for Study Drug Discontinuation: If methemoglobin > 7% is sustained or severe respiratory failure, multi-organ failure and/or other conditions arise that impair the ability of the subject to receive INOpulse, INOpulse therapy should be permanently discontinued. Severe respiratory failure does not include subjects that require use of High Flow Nasal Cannula ≤ 15L/minute (these subjects can continue to receive INOpulse treatment).

10.1.13. Laboratory Evaluation

The following blood tests will be performed locally: CBC with differential, chemistry panel (sodium, potassium, chloride, CO2, BUN, creatinine, glucose), LFTs (AST/ALT and total bilirubin), troponin (High Sensitivity Cardiac Troponin [Hs-cTN]), D-Dimer, NT-pro-BNP (if NT-pro-BNP is not available locally, BNP can be drawn and converted using the online calculator: https://www.cardio.med.tohoku.ac.jp/calc/nt-probnp.html), LDH, fibrinogen, ferritin, triglycerides and pro-calcitonin.

If available at the local lab, also include CRP, Von Willebrands Factor, Factor VIII Activity, Protein C, Protein S, Homocysteine, Antithrombin 3, Thrombelastography (TEG), G6PD deficiency and Prothrombin gene G2021A.

Lab results obtained within the previous 48 hours of randomization are acceptable for screening purposes if there has not been a significant change in the subject's clinical status.

10.1.14. Symptomatic Rebound Testing Post INOpulse Discontinuation

Subjects receiving INOpulse should be monitored every 30 minutes for 1 hour after discontinuation of treatment, including early discontinuation subjects, for signs and symptoms of rebound (eg, systemic arterial oxygen desaturation, hypoxemia, bradycardia, tachycardia, systemic hypotension, shortness of breath, near-syncope, and syncope). If symptomatic rebound is observed, treatment with INOpulse should be re-started and the Investigator should contact Bellerophon.

10.1.15. Adverse Events

Adverse events, including serious AEs, will be assessed daily while hospitalized and at all study visits until End of Study. If an AE or SAE 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.

10.1.16. Drug Dispensing – Treatment Period

Prior to drug administration, the INOpulse® delivery device will be programmed and set up as per the INOpulse® Instructions for Use. Subjects will be instructed to notify the clinic staff if they hear an audible alert tone and/or if they notice flashing/steady amber or red lights from the INOpulse® delivery device during drug administration. Subjects will use the INOpulse for 24 hours daily until resolution of hypoxemia, protocol defined respiratory failure, hospital discharge or Day 28, whichever occurs first. In instances where continuous INOpulse dosing is not feasible (eg, due to PPE limitations), INOpulse should be used a minimum of 12 hours daily. Subjects may use 1 to 4 cartridges daily depending upon the duration of treatment (maximum of 28 days).

Safety will be assessed throughout the study by monitoring vital signs, methemoglobin, SpO_2 and adverse events.

All devices and cartridges will be returned to the Sponsor at the end of the study.

10.1.17. INOpulse Device Usage Download

Treatment usage will be automatically monitored by the INOpulse device. Following administration of the last dose of INOpulse, site research team personnel will download the usage data from the INOpulse device on the same day. In the event that the INOpulse device is returned to the Sponsor rather than the site, the usage data will be downloaded by the Sponsor or designee.

11. INOPULSE INVESTIGATIONAL STUDY DRUG AND DEVICE

Subjects will be treated by means of an INOpulse device using an INOpulse cannula.

11.1. Inhaled Nitric Oxide

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).

Matching placebo will be supplied in size 0.074 liter aluminum cartridge containing N2, 99.999% gas, identical to that of the active drug cartridge (iNO 125) to ensure double-blind is maintained.

The study subject's characteristics that are used by the INOpulse device to administer the study drug at the appropriate dosage, i.e., the subject's sex and height, will be assessed during screening and verified by research staff in order to confirm the INOpulse device is programmed correctly.

INOpulse cannot be used concurrently with PAP or PEEP.

INOpulse cartridges will be labelled for the PULSE-CVD19-001 program. All cartridges will meet the requirements for this clinical trial.

The investigational study drug, iNO, will be manufactured by Mallinckrodt Pharmaceuticals located in Part Allen, Louisiana USA.

11.2. INOpulse Device Description and Operation

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

11.3. Packaging and Labeling of Study Products

INOpulse 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 in accordance with all legal and regulatory requirements of each country in which the study is being performed.

11.3.1. 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, the INOpulse study drug cartridges and devices should be stored in a secured, temperature controlled, and limited access area.

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

11.3.2. Dispensing

Only subjects participating in the study may receive INOpulse study drug and device. Authorized, medically trained research team members will initially administer the INOpulse study drug and device to subjects.

The study subject's characteristics that are used by the INOpulse device to administer 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 confirm the INOpulse device is programmed correctly. The IRT will determine the treatment group and will be used to capture the parameters that should be set in the INOpulse device.

11.3.3. 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

Electronic systems 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 INOpulse study drug and device accountability records documenting date, quantities, and unique identification numbers of supplies received, dispensed, returned, and accounts of any INOpulse 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 INOpulse 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).

11.4. INOpulse Study Drug and Device Disposition

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

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

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

12.1. Randomization and Blinding

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.

Blinded study drug should be started at the Baseline/Randomization 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 in the blinded treatment phase. 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. 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 INOpulse devices will be uniquely identified, and tracked and controlled by the IRT.

12.2. 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 CRF, and the Sponsor's medical monitor must be informed as soon as possible.

12.3. Interactive Response Technology (IRT)

Selected individuals at each study center will be authorized to have password protected access to the designated portions of the IRT 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, dose cohorts, and INOpulse drug/device supplies.

13. ADVERSE EVENTS AND DEVICE DEFICIENCIES

At each study, 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 most current MedDRA classification.

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.

13.1. Definitions

13.1.1. 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.

13.1.2. 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.

13.1.3. 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.

13.1.4. 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.

13.1.4.1. 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.

13.1.5. 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.

If the subject develops respiratory failure, as defined in this protocol, it will be considered an 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.

13.1.6. 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.

13.1.7. 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.

13.1.8. 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.

13.2. Severity and Causality Assessment for Adverse Events

13.2.1. 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

13.2.2. 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:

Not related: An AE that is clearly and incontrovertibly due to extraneous causes (disease, environment, other drugs etc.)

Unlikely related: An AE may be considered unlikely related if:

- Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)
- Disease or other drugs provide plausible explanations

Possibly related: 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.

Related: 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.

13.3. Outcome Assessment for Adverse Events

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

- Fatal
- Not recovered/not resolved
- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolved
- 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.

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

13.4.1. 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 at screening run in 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. All medical device deficiencies associated with a SAE will be coded and reported as required.

13.4.2. 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 and upon request of the Sponsor, the remaining investigational product study materials must be returned to the Sponsor and/or their designee for further investigation.

13.4.3. 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 using the SAE form at the study site **within 24 hours** of the site staff becoming aware of the event or investigational medical device deficiency.

The initial SAE report should include a detailed description of the event including start and stop dates, relationship, severity, and outcome assessments by the Investigator. All necessary information including laboratory test results and diagnostic information should also be provided

when reporting the SAE or providing follow-up. 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.

13.4.3.1. 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.

13.4.3.2. 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.

13.5. Data Monitoring Committee

An independent DMC will monitor and review data periodically throughout the trial, at a minimum monthly, as described in the DMC charter (Version 6.0 07 July 2020). The DMC will alert the Sponsor if there is any safety concern based on the provided data and will also advises on the appropriateness of continuing the study based on the DMC charter and in accordance with the statistical analysis plan. All SAEs will be sent to the DMC in a timely manner for review. A DMC charter will be developed with input from the DMC committee members, the SC and the Sponsor.

13.6. 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.

14. DATA MANAGEMENT AND RECORDKEEPING

14.1. 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.

Entered data will be reviewed 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.

14.2. 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.

14.3. 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.

14.4. 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.

14.5. 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.

15. 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.

15.1. 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), FDA Guidance for Industry, Investigators, and Institutional Review Boards, on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency, as well as any other elements required by state, local and institutional policies and applicable ISO standards.

Due to the infectious nature of COVID-19 and subjects in COVID-19 isolation, subjects may provide consent:

- using electronic methods, if such technology is available, or
- if electronic consenting is not available, a standard process should be implemented to obtain subject informed consent, consistently.

A copy of the informed consent document signed by the investigator and witness should be placed in the subject's source documents after the subject has had adequate time to ask questions and consider their participation in the study, with a note by the investigator of how the consent was obtained (eg, telephone call). The study record at the investigational site should document how it was confirmed that the subject signed the consent form (ie, either using attestation by the witness and investigator or the photograph of the signed consent). The note should include a statement of why the informed consent document signed by the subject was not retained (eg, due to potential contamination of the document by infectious material).

Consent must be obtained before any protocol related procedures that are not part of the subject's normal care. The date and time the consent was finalized should be recorded in the subject's medical chart. The subject must receive a copy of a dated, and signed consent form according to ICH GCP guidelines. 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 informed consent renders the subject ineligible for the study.

15.2. Independent Ethics Committee/Institutional Review Board

15.2.1. 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.

16. 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 18 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 90 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.

17. 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.

17.1. Primary Efficacy Analysis:

The primary analysis will be analyzed using a logistic regression model (Agresti, 2007, John Wiley and Sons) with treatment, age, gender and baseline stratification factors (used for stratified randomization) as covariates. Supportive analysis may be carried out while including other baseline subject level and site level covariates as needed (to be specified in the SAP).

The primary analysis is conducted at Day 28, however, we plan to conduct sensitivity analysis at Day 7 and Day 14 and day of discharge.

In addition, where appropriate, we plan to conduct time to event analysis to supplement the proportional analyses.

Details around the analysis plan will be provided in the SAP.

Expected Sample-Size

Initial assessment of the sample size is based on the historical experience of ~30% of hospitalized COVID-19 subjects deteriorating to needing increased respiratory support and the experience in our Emergency Expanded Access that indicates ~15% deteriorate.

Using 30% for the placebo arm and 15% for the iNO arm results in a sample size of 382 for a 1:1 randomized trial with 90% power for one-sided p-value of 0.025.

Based on this analysis, we are targeting a sample size of ~500 subjects. However, we note that the sample size may need to be re-assessed as the data on COVID-19 is rapidly evolving.

17.2. Interim Analysis:

An interim analysis for futility is planned after ~100 subjects have completed assessments through Day 28 in order to assess the failure rate in the iNO group versus placebo for the primary endpoint (death and respiratory failure). The interim analysis will be carried out by an independent external DMC based on pre specified criteria and stopping rules as detailed in the SAP.

18. MONITORING PROCEDURES

18.1. 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.

19. RESPONSIBILITIES

19.1. 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 or as otherwise feasible based on current emerging guidelines provided by FDA on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency. 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.

19.2. Audits and Inspections

To ensure compliance with GCP and all applicable regulatory requirements, Bellerophon Pulse Technologies LLC may conduct a quality assurance audit with considerations under COVID-19 restrictions. 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).

19.3. 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.

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