16.1.1 Protocol and Protocol Amendments

This section contains the following documents:

APC-VPCOV-CLN-001 Clean-FINAL-22Jun2020

APC-VPCOV-CLN-001 Amend-1 21Jul2020-signed

APC-VPCOV-CLN-001 Amend-2 03Nov2020-Clean-Final

APC-VPCOV-CLN-001 Amend-3 14Dec2020-Clean-Final

PROTOCOL TITLE	**TITLE: OPEN LABEL STUDY TO ASSESS THE EFFICACY AND SAFETY OF VENTAPROST (INHALED EPOPROSTENOL DELIVERED VIA DEDICATED DELIVERY SYSTEM) IN SUBJECTS WITH COVID-19 REQUIRING MECHANICAL VENTILATION**
PROTOCOL NUMBER	APC-VPCOV-CLN-001
INVESTIGATIONAL PRODUCT	VentaProst™
INDICATION	Reduction of respiratory, cardiac or circulatory failure in patients with COVID-19
PHASE	Phase 2a
SPONSOR	Aerogen Pharma Limited 1660 S Amphlett Boulevard, Suite 360 San Mateo, CA 94402 United States
MEDICAL MONITOR	Veronica Franco, MD, MSPH
APPROVAL DATE	22 June 2020
GCP STATEMENT	This study is to be performed in full compliance with International Conference on Harmonization (ICH) and all applicable local Good Clinical Practices (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
CONFIDENTIALITY STATEMENT	This document is confidential as it contains proprietary information of Aerogen Pharma. Any viewing or disclosure of such information that is not authorized in writing by the Aerogen Pharma is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

SPONSOR PROTOCOL APPROVAL PAGE

PROTOCOL TITLE	**AN OPEN LABEL STUDY TO ASSESS THE EFFICACY AND SAFETY OF VENTAPROST (INHALED EPOPROSTENOL DELIVERED VIA DEDICATED DELIVERY SYSTEM) IN SUBJECTS WITH COVID-19 REQUIRING MECHANICAL VENTILATION**
PROTOCOL NUMBER	**APC-VPCOV-CLN-001**
APPROVAL DATE	**22 June 2020**

22Jun2020

Judy Doto, RN, BSN — Date
Head of Clinical Operations
Aerogen Pharma

22 JUN 2020

Jim Fink PhD, RRT, FCCP — Date
Chief Scientific Officer
Aerogen Pharma

22 JUN 2020

Plamena Entcheva-Dimitrov, PhD, RAC — Date
Head of Regulatory and Medical Affairs
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Andy Clark 22 Jun 2020

Andy Clark PhD — Date
Vice President and General Manager
Aerogen Pharma

INVESTIGATOR'S SIGNATURE PAGE

PROTOCOL TITLE	**AN OPEN LABEL STUDY TO ASSESS THE EFFICACY AND SAFETY OF VENTAPROST (INHALED EPOPROSTENOL DELIVERED VIA DEDICATED DELIVERY SYSTEM) IN SUBJECTS WITH COVID-19 REQUIRING MECHANICAL VENTILATION**
PROTOCOL NUMBER	**APC-VPCOV-CLN-001**
APPROVAL DATE	**22 June 2020**

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with ICH-GCPs and all applicable local guidelines.

_____

Principal Investigator (printed/typed)

_____

Principal Investigator Signature Date

1. CLINICAL PROTOCOL SYNOPSIS

<table>
<tr><td>Sponsor</td><td>Aerogen Pharma</td></tr>
<tr><td>Protocol No.</td><td>APC-VPCOV-CLN-001</td></tr>
<tr><td>Title of Study</td><td>Open label study to assess the efficacy and safety of VentaProst (Inhaled epoprostenol delivered via dedicated delivery system) in subjects with COVID-19 requiring mechanical ventilation.</td></tr>
<tr><td>Study Centers</td><td>One clinical site in the US</td></tr>
<tr><td>Phase</td><td>Phase 2a</td></tr>
<tr><td>Objectives</td><td>Primary Objective:
The primary objective of this study is the reduction of respiratory, cardiac or circulatory failure in patients with confirmed COVID-19.
Secondary Objectives:
The secondary objective in this study is to evaluate the effects of VentaProst on improvement in oxygenation and improvement in clinical outcomes.

The study will also evaluate the effects of VentaProst on inflammatory parameters in subjects with confirmed COVID-19.</td></tr>
<tr><td>Study Design</td><td>This study will evaluate the potential therapeutic benefit of VentaProst in treating patients with COVID-19 at risk for the progression of respiratory and/ or cardiac/circulatory failure. This is an open label study of VentaProst in 10 confirmed COVID-19 patients compared to 20 COVID-19 historical control patients to assess the efficacy and safety of VentaProst at an initial dose of 13.6 ng/kg/min (A range from 3.4-30.6 ng/kg/min may be administered based on the investigator discretion) for a maximum of 10 days at the discretion of the Investigator. The patient will be followed through Day 28 to assess clinical outcomes.
Patients will be enrolled into the study within 24 hours of being placed on a mechanical ventilator. Patients will be administered VentaProst using the dedicated delivery system which allows up and down titration of the inhaled epoprostenol to achive hemodynamic and oxygenation stability. The starting dose will be initiated at 13.6 ng/kg/min. Based on hemodynamic and oxygenation parameters, the dose can be increased in 3.4 ng/kg/min increments up to a maximum of 30.6 ng/kg/min or down to a minimum of 3.4 ng/kg/min. The titration table below shows the typical up titration and also shows downward titration steps for VentaProst while patients are on mechanical ventilation.
Table 1: Overview of Titration and Weaning Guidelines
<table>
<tr><th>Uptitration Guideline</th><th>Downward Titration / Weaning Guideline*</th></tr>
<tr><td>Start Dose: 13.6 ng/kg/min</td><td>Start Dose: 13.6 ng/kg/min</td></tr>
<tr><td>1st Step Up Dose (17.0)</td><td>1st Step Down dose (10.2)</td></tr>
<tr><td>2nd Step Up Dose (20.4)</td><td>2nd Step Down Dose (6.8)</td></tr>
<tr><td>3rd Step Up Dose (23.8)</td><td>3rd Step Down dose (3.4)</td></tr>
</table></td></tr>
</table>

	<table><tr><td>4th Step Up Dose (27.2) 5th Step Up Dose (30.6)</td><td></td></tr></table> *If the patient has been up-titrated weaning should occur from that level in 3.4 ng/kg/min decrements. Patients will be weaned from VentaProst slowly due to concern that VentaProst is providing significant clinical benefit and to avoid rebound vasoconstriction. During weaning, doses will be decreased in steps of 3.4 ng/kg/min increments, with a minimum of 15 minutes between changes. The VentaProst weaning process should occur in isolation to other treatment changes (no changes in inotropes, vasopressors, or vasodilators) whenever possible. Patients will be observed closely before, during, and after dose changes. In the event patients demonstrate signs of hemodynamic instability or a decrease in oxygenation indicated by pulse oximetry during downward titration, the VentaProst dose will be returned to its previous level. Once patients have been stable for at least 15 minutes, repeat attempts at dose reduction may be undertaken. The process will continue until patients are fully weaned from VentaProst. Patients will be monitored for safety and PD efficacy throughout VentaProst administration.
Number/Type of Patients	Approximately 30 patients will be enrolled in this study. 10 COVID-19 positive study participants will receive VentaProst and will be compared to 20 COVID-19 positive historical control patients who have received standard of care (SOC) therapy. For retrospective comparison, each treatment patient will be matched to 2 confirmed COVID-19 historical controls treated at the clinical center between February 2020 and end of this study using the following criteria whenever available: comparable age, similar degree of disease severity (e.g. similar organ damage, similar co-morbidities, similar oxygenation status), on Mechanical Ventilation in ICU.
Inclusion Criteria	Patients are eligible for this study if they meet all of the following criteria: 1. Women and Men Age ≥18 years old (no upper limit) 2. Confirmed COVID-19 positive by RT-PCR test 3. Patients who require invasive mechanical ventilation. 4. Enrolled into study within 24 hours of being placed on mechanical ventilation 5. Consent or professional consent obtained 6. Duration of shortness of breath must be within the previous 14 days. 7. Female subjects of childbearing potential must have a negative pre-treatment pregnancy test (serum or urine). 8. Willing and able to comply with treatment schedule and follow-up.
Exclusion Criteria	Patients are **NOT** eligible for this study if they meet any of the following criteria: 1. Patients on ECMO support. 2. Patients receiving another inhalation research medication or inhaled nitric oxide. 3. Not expected to survive for 48 hours. 4. Pregnant (positive pregnancy test in a pre-dose examination) or breastfeeding 5. Open tracheostomy. 6. Clinical contra-indication, as deemed by the attending physician. 7. Allergy to Epoprostenol and its diluent

	8. Using inhaled vasodilators at baseline. 9. Patients who are hemodynamically unstable as determined by investigator 10. Patients with significant hemoptysis as determined by investigator
Study Treatment(s)	Patients will receive VentaProst via mechanical ventilator, starting at 13.6 ng/kg/min. If determined by the treating physician, the VentaProst can be up titrated to 30.6 ng/kg/min (in 3.4 ng/kg/min increments). At the Investigator's discretion, the patient will be weaned off the drug in 3.4 ng/kg/min increments. Medication can be administered up to 10 days.
Duration of Treatment	The duration of study participation for each patient is as follows: • Screening: up to 14 days • Treatment: up to 10 days • Follow up: 28 days
Criteria for Evaluation	Primary Endpoint 1. Reduction of respiratory failure. Failure is defined by any one of the following: • Requires VV ECMO • Inability to extubate patient within 10 days or reintubation within < 24 hours • Change in S/F, oxygenation index and P/F ratio (≥15%) from baseline to 12 hours, Days 1, 2, 3, 4, 5, 6, 7, 8, 9 and Day 10 (or end of treatment) **or** 2. Reduction of cardiac or circulatory failure. Failure is defined by any one of the following: • Need to begin inotropic or 10% increase in current vasopressor therapy • Worsening hemodynamic parameters • Cardiac troponin > 20% from baseline • BNP ≥ 15% of baseline • Need for temporary mechanical circulatory support (IABP, Impella) • Requires VA ECMO Secondary Endpoints: 1. Improvement in oxygenation defined as any one of the following: • Stabilization of PaO2/FIO2 >250 • Improvement in FIO2 by 50% or improvements ≥15% in S/F, P/F ratio from baseline at 12 hours, Day 5 and Day 10 (or end of treatment) 2. Improved clinical outcomes defined as one of more of the following: • Shorter time to extubation following the site's extubation protocol • Free from reintubation • Reduction in ICU days • Reduction in the number of re-admissions to the ICU due to COVID-19 within 28 days. • Reduction in hospital days • Mortality (28 Days) defined as Cardiopulmonary mortality or mortality from all causes. 3. Safety and tolerability • Monitoring of adverse events (AEs), serious adverse events (SAEs), chest

	CT or Chest X-rays, vital signs, ventilatory and oxygenation parameters, and laboratory tests. **Exploratory endpoints will include (where available):** 1. Change in LDH 2. Change in fibrinogen 3. Change in WBC count including lymphocytes and neutrophil subsets 4. Change in triglycerides 5. Change in ferritin 6. Change in CRP / ESR 7. Change in IL-6 8. Change in D-Dimer
Ventilatory Parameters	<u>OSU SOC:</u> Ventilator Type (GE) Parameters to monitor are: 1. Ventilator Mode 2. FiO_2 3. Inspiratory Time 4. Mean Airway Pressure 5. Peak Inspiratory Pressure 6. Positive End Expiratory Pressure 7. Respiratory Rate 8. Tidal Volume
Criteria for Stopping VentaProst Treatment	**<u>Individual patients stopping criteria:</u>** At any time during VentaProst administration, patients may be removed from study treatment and placed on standard of care (SoC) therapy if they meet one or more of the following pre-defined criteria leading to a deterioration in their condition: • Severe hypotension as evidenced by a systolic BP < 90 mmHg or MAP < 60 mmHG for >2 hours from the start of VentaProst • Need for VV ECMO • Need to increase existing vasopressor therapy by more than 25% • Worsening in oxygenation, ventilatory, or hemodynamic parameters that in the opinion of the investigator the patient should be removed from study treatment • Hemoptysis • If a clinically inadequate response to VentaProst is observed **<u>Study stopping criteria:</u>** If 3 patients are removed from the study for any of the above conditions, the study will stop further enrollment and an investigation will be conducted to determine the cause of the events. An independent safety evaluation will also be conducted. If it is suspected that the investigational product has caused the events, the study will be terminated. **Independent Safety Evaluation:** Independent safety evaluation will be conducted by a licensed physician who is not involved in the VentaProst COVID-19 clinical study or the sponsoring organization.
Statistical Methods	All patients who are enrolled in the study and who receive at least one dose of VentaProst will be included in the intent-to-treat (ITT) analyses of pharmacodynamic and safety data. All available data will be used and missing data will not be estimated or carried forward in any

	statistical summary or analyses. Descriptive summary statistics include the number of patients, mean, median, percent coefficient of variation (% CV) (if required), standard deviation, and minimum and maximum values (quantitative variables) or the number of patients and percentages by category (qualitative variables). Changes will be assessed as the difference between baseline measurements and the appropriate post-dose measurements unless otherwise specified. Mean differences between active and historical control groups will be assessed and significance will be determined on the basis of a 95% CI. No formal estimate of the sample size has been made. This is an exploratory study and the number of patients was selected to enable an adequate clinical assessment of pharmacodynamic, safety, and tolerability parameters without presenting undue risk to a large number of patients.
Efficacy Analysis	Efficacy will be secondarily determined by summarizing success or failure to meet any of the primary or secondary endpoints as compared to the matching historical controls.
Safety Analyses	Safety data will be summarized for both treatment group and historical control (when available) group using frequencies and incidence rates. Safety will be assessed through monitoring of adverse events (AEs), serious adverse events (SAEs), chest CTs or chest X-rays, laboratory tests, oxygenation and ventilatory parameters, and vital signs.

Table 2: Schedule of Assessments and Procedures

	Screening	VentaProst - Day 1		VentaProst Days 2-10									End of Study
Study Procedures	**Within 14 Days Prior to Baseline**	**Baseline - 0 Hr**	**12 hrs**	**D-2**	**D-3**	**D-4**	**D-5**	**D-6**	**D-7**	**D-8**	**D-9**	**D-10**	**Day 28 (+/- 2 days)**
Written Informed Consent	X												
Demographics	X												
Medical History	X												
Review Inclusion/Exclusion Eligibility Criteria	X	X											
Medication History/ Prior Meds	X												
Physical Examination	X												
Weight/Height[1]	X											X	
Chest CT Scan or CXR	X						X						
Clinical Laboratory Sampling[2]	X		X				X					X	
Pregnancy Test (Serum or Urine)	X												
RT-PCR + for COVID-19	X						X					X	
Administer VentaProst		X	X	X	X	X	X	X	X	X	X	X	
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	
Oxygenation Measurements[4]		X	X	X	X	X	X	X	X	X	X	X	
Ventilator Parameters[5]		X	X	X	X	X	X	X	X	X	X	X	
AE/SAE Monitoring		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X
Prone position		X	X	X	X	X	X	X	X	X	X	X	

[1] Height only performed at screening

[2] Clinical Labs include: Safety labs: CBC (lymphocyte and neutrophil counts), Full Chemistry Panel (including LFTs) and PT/PTT drawn Screening, Day 1-12 hours, Days 5 & 10. Triglycerides, LDH, ferritin, fibrinogen, CRP, ESR, IL-6, D-Dimer, troponin, BNP drawn at Screening, Day 1-12 hours and Day 10.

[3] Vital signs: Prior to initiating VentaProst, Days 1-10 twice daily (morning and evening) at the same time to reduce exposure to Health Care Professionals to include; temperature, pulse rate, blood pressure.

[4] Continuous SpO2 via pulse oximetry

[5] Ventilator Parameters will be collected twice daily along with vital signs and include: Ventilator Type, Ventilator Mode, FiO_2, Inspiratory Time, Mean Airway Pressure, Peak Inspiratory Pressure, Positive End Expiratory Pressure, Tidal Volume and Respiratory Rate

[6] Time Prone Position – 16 hours per day per OSU protocol

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LIST OF ACRONYMS, ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
AE	Adverse |Event
ALI	Acute Lung Injury
ALT (SGPT)	Alanine Aminotransferase (serum glutamic pyruvic transaminase)
AP	Alkaline Phosphatase
ARDS	Acute Respiratory Distress Syndrome
AST (SGOT)	Aspartate Aminotransferase (serum glutamic oxaloacetic transaminase)
bpm	Beats Per Minute
BNP	Brain Natriuretic Peptide
BUN	Blood Urea Nitrogen
cAMP	Cyclic Adenosine Monophosphate
CI	Cardiac Index (L/min/m^2)
CO	Cardiac Output (L/min)
CFR	Code of Federal Regulations
C_{max}	Maximum Concentration
CPB	Cardiopulmonary Bypass
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-Reactive Protein
CSR	Clinical Study Report
CVP	Central Venous Pressure (mm Hg)
DCF	Data Collection Form
DNR	Do Not Resuscitate
dPAP	Diastolic Pulmonary Arterial Pressure (mm Hg)
dSAP	Diastolic Systemic Arterial Pressure (mm Hg)
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation

Abbreviation	Term
ESR	Erythrocyte Sedimentation Rate
ETT	Endotracheal Tube
FDA	Food and Drug Administration
FiO_2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
HME	Heat-Moisture Exchanger
HR	Heart Rate (bpm)
IABP	Intra-aortic Balloon Pump
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IL-6	Interleukin 6
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
LAR	Legally Authorized Representative
LDR	Lung Dosing Rate
LFT	Liver Function Test
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute
mPAP	Mean Pulmonary Arterial Pressure (mm Hg)
mSAP	Mean Systemic Arterial Pressure (mm Hg)
NC	Nasal Cannula
ng	Nanogram
OR	Operating Room
OTC	Over-the-Counter
PAH	Pulmonary Arterial Hypertension
PaO_2	Partial Pressure of Oxygen in Arterial Blood
PAP	Pulmonary Arterial Pressure (mm Hg)
PCWP	Pulmonary Capillary Wedge Pressure
PD	Pharmacodynamic
PEEP	Positive End Expiratory Pressure
PH	Pulmonary Hypertension
PIP	Peak Inspiratory Pressure
PK	Pharmacokinetic
PP	Per Protocol
PGI_2	Prostaglandin I_2 (epoprostenol)
PVR	Pulmonary Vascular Resistance (dyn/sec/cm^5)
RBC	Red Blood Cell (count)
RH	Right Heart
RHF	Right Heart Failure

Abbreviation	Term
RT-PCR	Reverse Transcription Polymerase Chain Reaction
RVSWI	Right Ventricular Stroke Work Index
SAE	Serious Adverse Event
SaO_2	Arterial Oxygen Saturation
sPAP	Systolic Pulmonary Arterial Pressure (mm Hg)
sSAP	Systolic Systemic Arterial Pressure (mm Hg)
SE	Standard Error
SOP	Standard Operating Procedures
SOC	Standard of Care
SpO_2	Oxygen Saturation by Pulse Oximetry
SVR	Systemic Vascular Resistance
TEAE	Treatment-Emergent Adverse Event
TEE	Transesophageal Echocardiogram
TPG	Transpulmonary Gradient
$t_{1/2}$	Half-Life
TLD	Total Lung Dose
ULN	Upper Limit of Normal
VA-ECMO	Veno-arterial Extracorporeal Membrane Oxygenation
VentaProst	VentaProst™ – Drug/device combination product consisting of aerosolized epoprostenol delivered via dedicated drug delivery system
VentaProst Nebulizer	The nebulizer assembly that is part of the VentaProst delivery system
VTE	Venous Thromboemobolism
VV ECMO	Venovenous Extracorporeal Membrane Oxygenation
WBC	White Blood Cell (count)
WHO	World Health Organization

BACKGROUND AND RATIONALE

2.1 Introduction

COVID-19 is a rapidly emerging pathogen that has recently been declared a pandemic by the World Health Organization (WHO). No targeted therapeutic treatments for coronavirus (COVID-19) have been identified. Symptoms range from mild upper respiratory tract infection to profound hypoxia, severe pneumonia, ARDS and death. Progression of end stage disease is unpredictable with high fatality rates in mechanically ventilated patients as a result of multi-organ failure. Among patients who require hospitalization, mortality may be 5% to 15%, and for those who become critically ill, reported mortality ranges from 22% to 62%.

Prostacyclin therapy—available in oral, inhaled, and intravenous forms—is an analogue which mimics endogenous prostacyclin (PGI2). Prostacyclin binds to its receptor (a G-protein coupled receptor) found on the surface of vascular smooth muscle and platelets, activates cyclic adenosine monophosphate (cAMP), and results in inhibition of platelet

aggregation, vascular smooth muscle relaxation and vasodilation of the pulmonary arteries (Mitchell, Ali et al. 2008). Prostacyclins are most commonly used in the treatment of PAH due to their potent vasodilatory effects. In addition, prostacyclin analogs also inhibit platelet aggregation and may reduce prothrombotic effects of endothelin.

The rationale for use of vasodilators in COVID-19 patients rests on their rapid local effect on the pulmonary vasculature, which has shown to lead to increased oxygenation in other diseases, such as PAH (Higenbottam, Wheeldon et al. 1984) and post-surgical PH (De Wet, Affleck et al. 2004). Epoprostenol has the additional advantage over inhaled nitric oxide in that it may be directly administered through a standard ventilator (closed-circuit).

The rationale for aerosolized prostacyclin use in COVID-19 patients experiencing hypoxia leading to cardiac failure is two-fold:
(1) inhaled prostacyclin therapy has been used in the treatment of ARDS and has been shown to improve oxygenation and ventilation-perfusion mismatch (see Section 9). Prostacyclins, such as epoprostenol, promote pulmonary vasodilation via a cyclic adenosine monophosphate-mediated decrease in intracellular calcium (Figure 4). While it has not been associated with improved outcomes, such as mortality, and it's use in ARDS is off-label, it may be used in severe life-threatening hypoxemia refractory to conventional ARDS management, such as has been seen in COVID-19.
(2) The second potential benefit of prostacyclin therapy in the management of COVID-19 is to mitigate direct SARS-CoV-2-associated coagulopathy. Prostacyclins have anti-inflammatory (Dewachter 2012) and antiplatelet aggregation properties[1]. Microvascular thrombosis and large vessel venous thromboembolism have been described anecdotally and in case reports of corona virus infected patients and abnormal coagulation parameters are associated with increased mortality (Giannis, Ziogas et al. 2020). Inhibition of platelet aggregation occurs with prostacyclin therapy and may mitigate thrombosis in situ seen in PAH itself, and potentially in patients with COVID-19 associated respiratory illness.
Literature data with both inhaled NO and inhaled epoprostenol in ARDS, acute lung injury and severe hypoxemia show improvement of oxygenation (Afshari, Bastholm Bille et al. 2017), (Dzierba, Abel et al. 2014), decrease of pulmonary arterial pressure (Fuller, Mohr et al. 2015) and in some cases improvement in clinical outcomes such as shorter time on mechanical ventilation and shorter time in ICU (Ammar, Bauer et al. 2015). However, due to the heterogeneity of the population and the severity of the disease, not all studies agree on the effectiveness of inhaled epoprostenol, particularly to reduce mortality in ARDS (Adhikari, Dellinger et al. 2014), (Afshari, Bastholm Bille et al. 2017). Meta-analyses have concluded that the quality of the currently published data for the use of inhaled vasodilators in ARDS, ALI and refractory hypoxemia is insufficient to definitely conclude for or against their use (Afshari, Bastholm Bille et al. 2017), (Fuller, Mohr et al. 2015).

This study will evaluate the potential therapeutic benefit of VentaProst in treating patients with COVID-19 at risk for the progression of respiratory and/or cardiac/circulatory failure. This open-label study will assess the efficacy and safety of VentaProst at a range of 3.4-30.6 ng/kg/min (based on the investigator discretion) for a maximum of 10 days at the discretion of the Investigator. The patient will be followed through Day 28 to assess

their clinical status.

2.2 VentaProst

2.2.1 Nonclinical Experience

Refer to the current Investigator's Brochure (IB) for details of nonclinical pharmacology and toxicology studies with VentaProst.

2.2.2 Clinical Experience

There have been no clinical trials to date with VentaProst in COVID-19 patients (see Section 2.2.4 below for summary of clinical data with VentaProst in cardiac surgery patients).

2.2.3 Summary of Pharmacokinetic Results

Epoprostenol undergoes rapid chemical hydrolysis under physiological conditions to yield 6-keto-PGF1α and is also subject to enzymatic degradation. As such, it is only possible to evaluate the PK using radioactively labeled drug. Studies using 3H-epoprostenol sodium indicate half-life is generally less than 3 minutes with an I.V. bolus, and with I.V. infusion, plasma steady-state concentrations were achieved within 15 minutes of initiation of the infusions, and steady-state concentrations increased linearly with increasing infusion rate. Tissue distribution studies indicate the highest levels of radioactivity were observed in the kidney, liver, and small intestine and the lowest levels were observed in brain and adipose tissue. Epoprostenol-derived material is rapidly excreted into urine and feces after dosing with epoprostenol sodium.

There is only one study in the literature that reports the PK of inhaled epoprostenol. The study by Haraldsson (Haraldsson, Kieler-Jensen et al. 2000) was designed to evaluate the effects of inhaled epoprostenol on platelet aggregation after surgery. No differences were seen in 6-keto-PGF1α levels with two dose levels of epoprostenol compared to placebo over six hours of administration in the ICU. Epoprostenol deposition in the lungs was not quantified, but the aerosol was administered only during the inspiratory phase of mechanical ventilation. The blood levels of 6-keto-PGF1α by enzyme immunoassay in this study were reported to be several times higher than other levels reported in the literature.

In 2017, Stanford University's Department of Cardiac Surgery conducted an observational study (IND129777, Report# APC-VP-CLN-004) investigating the levels of 6-keto-PGF1α in cardiac surgery patient requiring CPB. Sixteen patients were enrolled; eight did not received inhaled epoprostenol, eight received aerosolized epoprostenol at a nominal starting dose of 50 ng/kg/min.

Plasma levels determined in aerosol epoprostenol naïve patients indicates that cardiac surgery procedures, including CPB, result in elevated endogenous levels of both 6-keto-PGF1α and thromboxane B2. Delivery of aerosol epoprostenol in patients resulted in a further elevation of 6-keto-PGF1α levels, but not thromboxane B2.

While it proved difficult to delineate the endogenous and exogenous contributions of

aerosol delivery during surgery, 6-keto-PGF1α levels declined rapidly in aerosol naïve patients during ICU stay. Examination of the 6-keto-PGF1α levels during weaning, after this endogenous decline, indicate that the overall aerosol delivery efficiency, nebulized to absorbed (deposited lung dose), is less than 8%. That is, out of a nominal dosing rate of 50 ng/kg/min only 4 ng/kg/min actually reaches the lungs and gets absorbed.
Comparison to recently published data (Nicolas, Krause et al. 2012) investigating 6-keto-PGF1α levels during steady state I.V. administration of Flolan indicates that the systemic exposure from aerosol delivery in cardiac surgery is similar to, or lower, than that experienced from intravenous administration of the approved Flolan product.

The findings of this observational PK study with inhaled epoprostenol are sufficient to make a correlation to historical systemic exposure levels with intravenous administered Flolan (the reference listed drug) and show levels of exposure similar to, or lower than, the currently approved intravenous product.

2.2.4 Summary of Clinical Results

The safety and tolerability of VentaProst were evaluated in a Phase 2a Clinical Study in cardiac surgery patients "*A Two-Part Pharmacodynamic Study to Compare VentaProst™ (Epoprostenol Solution for Inhalation via Custom Drug Delivery System) Dosing to Conventionally Administered Aerosolized Epoprostenol Dosing in Cardiac Surgery Patients*" (NCT03122730).

Overall, 15 patients were exposed to doses of VP from 3.4 to 20.4 ng/kg/min in this study. Administration of VP in this dose range was well-tolerated. Overall, there were 2 patients (28.6%) in Part I and 1 patient (12.5%) in Part II who experienced a total of 7 TEAEs. All 7 TEAEs were assessed by the investigator as related to the surgical procedure and as unrelated to the study drug and unrelated to the device. No deaths occurred during the study. A total of 3 patients had 1 SAE each. All 3 SAEs were considered to be unrelated to the study drug or the study device.

Seven patients were evaluated in Part I to determine the effective dose equivalence between VP delivered at 17 ng/kg/min and off-label aerosolized Veletri administered at 50 ng/kg/min during mechanical ventilation. In all patients, VP 17 ng/kg/min was found to be equivalent either by calculation of effect compared with aerosolized Veletri 50 ng/kg/min or the investigators' judgement. In most patients, no differences were observed in oxygen saturation ranges between VP and aerosolized Veletri treatments at the same FiO2 while on the ventilator. The investigator determined that oxygenation, assessed by oxygen saturation measurements, did not change disproportionately with ventilator operating parameters on VP compared with aerosolized Veletri.

Eight patients were evaluated in Part II of the study to identify the optimal dose of VP. In the investigator's judgement, the optimal VP dose was determined to be 6.8 ng/kg/min in 2 patients, 10.2 ng/kg/min in 3 patients, and 13.6 ng/kg/min in 3 patients, which is the minimal dose that reliably produced a maximum hemodynamic response in all patients.

There have been no clinical trials to date with VentaProst in COVID-19 patients.

See IB for additional clinical information regarding inhaled epoprostenol.

2.2.5 Summary of Known and Potential Risks of Inhaled Epoprostenol Administration

Safety of inhaled epoprostenol in cardiothoracic surgery patients is remarkable. In the reported literature to date, there were no reports of serious or life-threatening drug-related safety events. Due to its mechanism of action, inhaled epoprostenol may theoretically cause increased bleeding (anti-platelet mechanism) or systemic vasodilation consequent to spill over into the central circulatory system, but no such events have been reported. Some accounts of the use of inhaled prostacyclin in the chronic setting (e.g. iloprost for PAH) report transient events as listed on the approved product labeling. These include cough, headache, flushing, and an influenza-like syndrome. However, these types of events are unlikely to be reported due to sedation in the ICU setting.

VentaProst may result in hypotension, which will be monitored via frequent - assessments of oxygenation, ventilatory and hemodynamic parameters and vital signs. Worsening oxygenation is a theoretic concern through worsened ventilation/ perfusion matching. This will be monitored through continuous pulse oximetry throughout the administration of the inhaled epoprostenol.

Risks to subjects in this study are related to common procedures performed (e.g., venipuncture) and the documented adverse events (AEs) listed in the current Investigator's Brochure. These risks are communicated to the subjects in the consent forms. There may be additional risks that are currently unknown.

The benefits of the study may include targeted lung vasodilation and improved oxygenation, potential anti-platelet effects on the lung vasculature, reduction in disease progression, avoidance of greater oxygen needs and early weaning off mechanical ventilation. If the drug does have such properties, then this may aid recovery, improve outcomes and enable an earlier discharge from the hospital.
There is no funding awarded to the patients participating in this study.

2.2.6 Dosing Rationale for VentaProst

Literature on the current use of aerosolized epoprostenol in cardiac surgery and in ARDS shows a wide range and technically variable dosing for lowering PVR (Rao, Ghadimi et al. 2018), (Kallet, Burns et al. 2017), (Fuller, Mohr et al. 2015). Most of the experience is with continuous nebulization by commercially available nebulizers in various positions in mechanical ventilator circuits at doses of 50 ng/kg/min. Unlike the commercially available nebulizer systems, the VentaProst delivery platform aerosolizes epoprostenol only during the inspiratory cycle of the ventilator and administers respirable sized aerosol droplets (3-5 μm) in close proximity to the ETT of mechanically ventilated patients.

The assumed effect of the current continuous dosing regimen of 50 ng/kg/min is that the hemodynamic response is maximized and that no further improvements would be seen by increasing the dose. The initial in vitro estimate of the equivalent VentaProst (VP) dose to a 50 ng/kg/min conventional dose of continuously aerosolized Veletri was 17

ng/kg/min, which was the starting dose in Part I of the APC-VP-CLN-001 Phase 2a study conducted by Aerogen Pharma. During Part I of the study, it was determined that this dose is equivalent to 50 ng/kg/min epoprostenol delivered off-label via a generic nebulizer and continuous delivery. In Part II of the APC-VP-CLN-001 Phase 2a study, the VP dose escalation started from an initial dose of 3.4 ng/kg/min (20% of the equivalent dose). The dose was then increased in 3.4 ng/kg/min increments. Part II of the study was designed to demonstrate that the dose-response plateau could be achieved using lower VP doses than the initial estimated equivalent dose in Part I. Doses up to 30.6 ng/kg/min were approved for use in the study. In Part I of the study one patient, per the investigator discretion, received a 20.4 ng/kg/min dose. In Part II of the study it was determined that the optimal VP dose of 6.8 ng/kg/min in 2 patients, 10.2 ng/kg/min in 3 patients, and 13.6 ng/kg/min in 3 patients provided stable hemodynamic response. Based on these data, the recommended starting dose of VP, will be 13.6 ng/kg/min, as this dose is anticipated to produce the maximum hemodynamic response.

The proposed nominal dosing regimen for this COVID-19 trial is for up to 10 days of breath-synchronized aerosol delivery with a starting dose of 13.6 ng/kg/min drug and range between 10.2 and 30.6 ng/kg/min. Lower doses can also be used depending on the clinical state of the patient and the discretion of the physician. Of this nominal dosing rate approximately 30% will reach and deposit in the lung. Thus, the maximum Lung Dosing Rate (LDR) is ~10 ng/kg/min and the maximum Total Lung Dose (TLD) is ~ 144 μg/kg (Refer to VP IB Edition 6 dated 17-Jun-2020).

The inhalation toxicology program for VentaProst, originally designed for the cardiac surgery indication, covered a maximum LDR of 320 ng/kg/min and 60 ng/kg/min and a maximum TLD of 1091.4 μg/kg and 172.8 μg/kg in rats and dogs respectively. The LDR and TLD margins over the proposed maximum clinical exposure are thus 32 and 6, and 7.6 and 1.2, in rats and dogs respectively.

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is the reduction of respiratory, cardiac or circulatory failure in patients with confirmed COVID-19.

3.2 Secondary Objectives

The secondary objective in this study is to evaluate the effects of VentaProst on improvement in oxygenation, improvement in clinical outcomes and safety and tolerability.

The study will also evaluate the effects of VentaProst on inflammatory parameters in subjects with confirmed COVID-19.

3.3 Study Design

This study will evaluate the potential therapeutic benefit of VentaProst in treating patients with COVID-19 at risk for the progression of respiratory and/or cardiac/circulatory failure. This is an open label study of VentaProst in 10 confirmed COVID-19 patients compared to 20 historical control confirmed COVID-19 patients to assess the efficacy and safety of VentaProst. Patients will be enrolled within 24 hours of being placed on mechanical ventilation and may have VentaProst given for up to 10 days. The patient will be followed through Day 28 to assess clinical outcomes.

The proposed dosing regimen for the COVOD-19 trial is for up to 10 days of breath-synchronized aerosol delivery with a starting dose of 13.6 ng/kg/min drug. Based on hemodynamic and oxygenation parameters, the dose can be titrated in 3.4 ng/kg/min steps up to a maximum of 30.6 ng/kg/min or down to a minimum of 3.4 ng/kg/min while patients are on mechanical ventilation. Titration guidelines are provided in Section 5.3.3.

Patients will be weaned from VentaProst slowly due to concern that VentaProst is providing significant clinical benefit and to avoid a rebound vasoconstriction. During weaning, doses will be decreased in steps of 3.4 ng/kg/min increments, with a minimum of 15 minutes between changes. The VentaProst weaning process should occur in isolation to other treatment changes (no changes in inotropes, vasopressors, or vasodilators) whenever possible. Patients will be observed closely before, during, and after dose changes. In the event patients demonstrate signs of hemodynamic instability or a decrease in oxygenation by pulse oximetry during downward titration, the VentaProst dose will be returned to its previous level. Once patients have been stable for at least 15 minutes, repeat attempts at dose reduction may be undertaken. The process will continue until patients are fully weaned from VentaProst. Patients will be monitored for safety and efficacy throughout VentaProst administration.

3.4 Duration of Participation

Patients who meet entry criteria will be entered into the study and the duration of study participation for each patient is listed below. The duration of study participation for each patient is as follows:

- Screening: up to 14 days

- Treatment: up to 10 days
- Follow up: 28 days

4. SELECTION AND WITHDRAWAL OF PATIENTS

Approximately 30 patients will be enrolled in this study. Ten study participants with a positive RT-PCR for COVID-19 and are mechanically ventilated will receive VentaProst and will be compared to twenty matching historical control patients with a positive RT-PCR for COVID-19 who have received standard of care (SOC) therapy.

Each treatment patient will be matched to 2 confirmed COVID-19 historical controls treated at the clinical center between February 2020 and end of this study using the following criteria whenever available: comparable age, similar degree of disease severity (e.g. similar organ damage, similar co-morbidities, similar oxygenation status), on Mechanical Ventilation in ICU.

Patients who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study medication.

4.1 Inclusion Criteria

Patients are eligible for this study if they meet all of the following criteria:

1. Women and Men Age ≥18 years old (no upper limit)
2. Confirmed COVID-19 positive by RT-PCR test
3. Patients who require invasive mechanical ventilation.
4. Enrolled into study within 24 hours of being placed on mechanical ventilation
5. Consent or professional consent obtained
6. Duration of shortness of breath must be within the previous 14 days.
7. Female subjects of childbearing potential must have a negative pre-treatment pregnancy test (serum or urine).
8. Willing and able to comply with treatment schedule and follow-up.

4.2 Exclusion Criteria

Patients are **NOT** eligible for this study if they meet any of the following criteria:

1. Patients on ECMO support.
2. Patients receiving another inhalation research medication or inhaled nitric oxide.
3. Not expected to survive for 48 hours.
4. Pregnant (positive pregnancy test in a pre-dose examination) or breastfeeding
5. Open tracheostomy.
6. Clinical contra-indication, as deemed by the attending physician.
7. Allergy to Epoprostenol and its diluent
8. Using inhaled vasodilators at baseline.

9. Patients who are hemodynamically unstable as determined by investigator
10. Patients with significant hemoptysis as determined by investigator

4.3 Re-Screening of Patients

Patients may not be enrolled more than once.

4.4 Removal of Patients from Therapy or Assessment

Aerogen Pharma or the Investigator may discontinue patients from the study at any time for safety or administrative reasons.

The End of Treatment Study procedures (at Day 10) are to be completed for all patients who discontinue from the study (except Screen Failure patients).

The Investigator will promptly explain to the patient or their LAR that the study will be discontinued for the patient and provide appropriate medical treatment and other necessary measures for the patient.

Patients who discontinue early from the study will be discontinued for one of these primary reasons: Adverse events, patient death, lost to follow-up, patient withdrew consent, protocol violation, lack of efficacy, investigator decision, study terminated by sponsor, screen failure, or other. Study disposition information will be collected on the Patient Disposition DCF.

4.4.1 Criteria for Stopping VentaProst Treatment

Individual patients stopping criteria: At any time during VentaProst administration, patients may be removed from study treatment and placed on standard of care (SoC) therapy if they meet one or more of the following pre-defined criteria leading to a deterioration in their condition:

- Severe hypotension as evidenced by a systolic BP < 90 mmHg or MAP < 60 mmHG for >2 hours from the start of VentaProst
- Need for VV ECMO
- Need to increase existing vasopressor therapy by more than 25%
- Worsening oxygenation, ventilatory, or hemodynamic parameters that in the opinion of the investigator the patient should be removed from study treatment
- Hemoptysis
- If a clinically inadequate response to VentaProst is observed

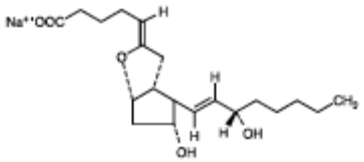
Study stopping criteria: If 3 patients are removed from the study for any of the above conditions, the study will stop further enrollment and investigation will be conducted to determine the cause of the events. An independent safety evaluation will also be conducted. If it is suspected that the investigational product has caused the events, the study will be terminated.

Independent Safety Evaluation: Independent safety evaluation will be conducted by a licensed physician who is not involved in the VentaProst COVID-19 clinical study or the sponsoring organization.

5. STUDY TREATMENTS

5.1 Identity of Medication Component of the Investigational Product

The study medication of VentaProst, Flolan (epoprostenol sodium), is manufactured by GlaxoSmithKline and has been analyzed and released according to their specifications. The Flolan will be procured by OSU on behalf of Aerogen Pharma and stored in the Investigational Pharmacy. The labelling of Flolan for this clinical trial will follow the protocols and procedures set forth by OSU's Investigational Pharmacy. Aerogen Pharma will provide labels to the pharmacy for labeling Flolan after it has been reconstituted per the VentaProst COVID pharmacy manual.

Drug Substance Name	Epoprostenol Sodium
Chemical Name	5Z,9α,11α,13*E*,15*S*)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-1-oic acid.
Molecular Formula	$C_{20}H_{31}NaO_5$
Structural Formula	
Molecular Weight	374.45

5.1.1 Storage Condition

Both the vials of study medication and sterile diluent buffer should be stored between 20º to 25ºC (68º to 77ºF) with excursions permitted to 15° to 30°C (59° to 86°F) and kept in the supplied carton to protect the product from light. Study medication will be stored in a secure, controlled-access location at the study sites.

5.2 Treatments Administered

Patients will receive VentaProst via mechanical ventilator, at an initial dose of 13.6 ng/kg/min. If determined by the treating physician, the VentaProst can be up titrated to 30.6 ng/kg/min or down titrated to 3.4 ng/kg/min (in 3.4 ng/kg/min increments). At the Investigator's discretion, the patient will be weaned off the drug in 3.4 ng/kg/min decrements. VentaProst can be administered up to 10 days.

5.3 Study Medication Supply, Preparation, and Administration

5.3.1 Study Medication Supply

The medicinal component of VentaProst, Flolan, is already approved for I.V. delivery. The dosage form is a vial of 1.5 mg epoprostenol as a lyophilizate and the required pH 12

Sterile Flolan diluent per the currently approved packet insert (NDA20-444/ Supplement 24[1]). Flolan and its diluent are not re-formulated by Aerogen Pharma. Flolan is used with the same diluent system and reconstituted per the approved packet insert.
Flolan and diluent container closure (glass vial and stopper/crimp-pH 12 Sterile Diluent for Flolan comes in a plastic bottle for mixing) and secondary packaging (cardboard box) are not being altered, including the information on the vial and box label and the information in the approved Flolan packet insert. This preserves the approved drug labeling information per NDA 20-444.

The patient number, dose number, date and time of dose administration will be recorded in the study medication dispensing logs.

5.3.2 Study Medication Preparation

Refer to the VentaProst-COVID Pharmacy Manual for preparation of the study medication for aerosol administration.

Prior to use, reconstituted solutions of epoprostenol sodium must be protected from light and must be refrigerated at 2° to 8°C (36° to 46°F) if not used immediately. Do not freeze reconstituted solutions of epoprostenol sodium for injection and discard any reconstituted solution that has been frozen. Discard any reconstituted solution if it has been refrigerated for more than 8 days.

Freshly prepared reconstituted solutions or reconstituted solutions that have been stored at 2°C to 8°C (36°F to 46°F) for no longer than 8 days can be administered up to 48 hours at up to 30°C (86°F).

5.3.3 Study Medication Administration

In the ICU, patients will be started on an initial dose of VentaProst of 13.6 ng/kg/min to be administered through the VentaProst delivery system. The patient may have their VentaProst dose titrated up or down in 3.4 ng/kg/min increments (refer to VentaProst Pharmacy Manual) as clinically indicated every 5 to 15 minutes as clinically indicated to a dose range of 3.4-30.6 ng/kg/min.

Table 3: Medication Administration Titration Guidelines

Uptitration Guideline	Downward Titration / Guideline
Start Dose: 13.6 ng/kg/min 1st Step Up Dose (17.0) 2nd Step Up Dose (20.4) 3rd Step Up Dose (23.8) 4th Step Up Dose (27.2) 5th Step Up Dose (30.6)	Start Dose: 13.6 ng/kg/min 1st Step Down dose (10.2) 2nd Step Down Dose (6.8) 3rd Step Down dose (3.4)

[1] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020444s024lbl.pdf

5.3.4 Study Medication Weaning

Patients will be weaned from VentaProst slowly due to concern that VentaProst is providing significant clinical benefit and to avoid a rebound vasoconstriction. Doses will be decreased in steps of 3.4 ng/kg/min with a minimum of 15 minutes between changes until drug has been discontinued. The VentaProst weaning process should occur in isolation to other treatment changes (no changes in inotropes, vasopressors, or vasodilators) whenever possible. Patients will be observed closely before, during, and after dosing changes. In the event patients demonstrate signs of hemodynamic instability or a decrease in oxygenation indicated by pulse oximetry during downward titration, the VentaProst dose will be returned to its previous level. Once patients have been stable for at least 15 minutes, repeat attempts at dose reduction may be undertaken. The process will continue until patients are fully weaned from VentaProst. Patients will be monitored for safety and efficacy throughout VentaProst administration.

5.4 Identity of the Device Component of the Investigational Product

5.4.1 Identity of Device

The Phase 2a VentaProst drug delivery system is designed to accurately and precisely administer aerosol to the lungs of critically ill patients who require support via mechanical ventilation. The aerosol generator's fundamental operating mechanism and materials of construction will be similar to the 510(k)-cleared Aeroneb Solo System (K120939, K103635, K070642, Aerogen Ltd) and it is being designed for compatibility with the range of ventilators found in the OR and ICU.

5.4.1.1 VentaProst Aerosol Delivery to Ventilated Patients

The VentaProst clinical study drug delivery system (Figure 1) consists of reusable and single-patient use disposable elements:

1. Reusable multi-patient use components consist of two electronic controllers, Aerogen Solo Nebulizer Cable, and Sensirion Flow Sensor Cable. When used together, they synchronize aerosol generation with the patient's inspiratory pattern through a single-patient use, disposable administration kit.
    - Aerogen Pro-X, is a commercially available device (K120939[2]) cleared for use to continuously operate the disposable Aerogen Solo nebulizer. (item #1 Figure 1).
    - Aerogen Pharma Controller (AP Controller) is an investigational device, which synchronizes aerosol generation with the ventilator inspiratory cycle (item #2 on Figure 1). This controller was tested to demonstrate its safety for use under IND129777.

[2] The product names for the Aerogen commercial products changed from the term "***Aeroneb***", to the brand name "***Aerogen***". A Note to File was submitted to FDA and receipt was acknowledged by the Branch Office

- Aerogen Solo Nebulizer Cable
- Sensirion Flow Sensor Cable

2. Single-patient disposable kit:
   - Aerogen Solo nebulizer (item #3 on Figure 1) is a commercially available, low mass and low profile vibrating mesh aerosol generator (K070642) cleared for use with the Aerogen Pro-X controller and Aerogen Continuous Nebulization Tube Set (CNTS).
   - Aerogen CNTS and syringe (items #4 and 5 on Figure 1) is a commercially available device (K103635) cleared for use to connect to the Aerogen Solo and deliver medication from the drug reservoir (syringe) to the mesh the nebulizer.
   - Flow sensor and cable connected to the Aerogen Pharma Controller (AP Controller, item #7 on Figure 1). This is a new component of the system, which was tested to demonstrate safety for use in a clinical study.

The VentaProst delivery system will be used in conjunction with a commercially available and FDA-cleared syringe pump (item #8 on Figure 1). In general, any available syringe pump, which (1) is compatible with the Aerogen Continuous Nebulization Tube Set (CNTS syringe and tubing), and (2) is capable of delivering medication to the vibrating mesh nebulizer within the range of 0.4 to 2.4 mL/h as required to deliver the doses specified in the APC-VPCOV-CLN-001 Pharmacy Manual. For purposes of the VPCOV study, Aerogen Pharma will supply the Perfusor® Space Infusion Syringe Pump System from B.Braun (Figure 1). This particular syringe pump is FDA-cleared (K093913), it is compatible with the CNTS syringe (items #4 on Figure 1) and is able to deliver fluids in the rage of 0.4 to 2.4 mL/h. It is worth noting that on 11 April 2020, this pump received EUA for use in the tracheal delivery of continuous nebulized medications into a nebulizer to treat patients of all ages with or suspected of having the Coronavirus Disease 2019 (COVID-19)[3].

[3] https://www.fda.gov/media/136894/download

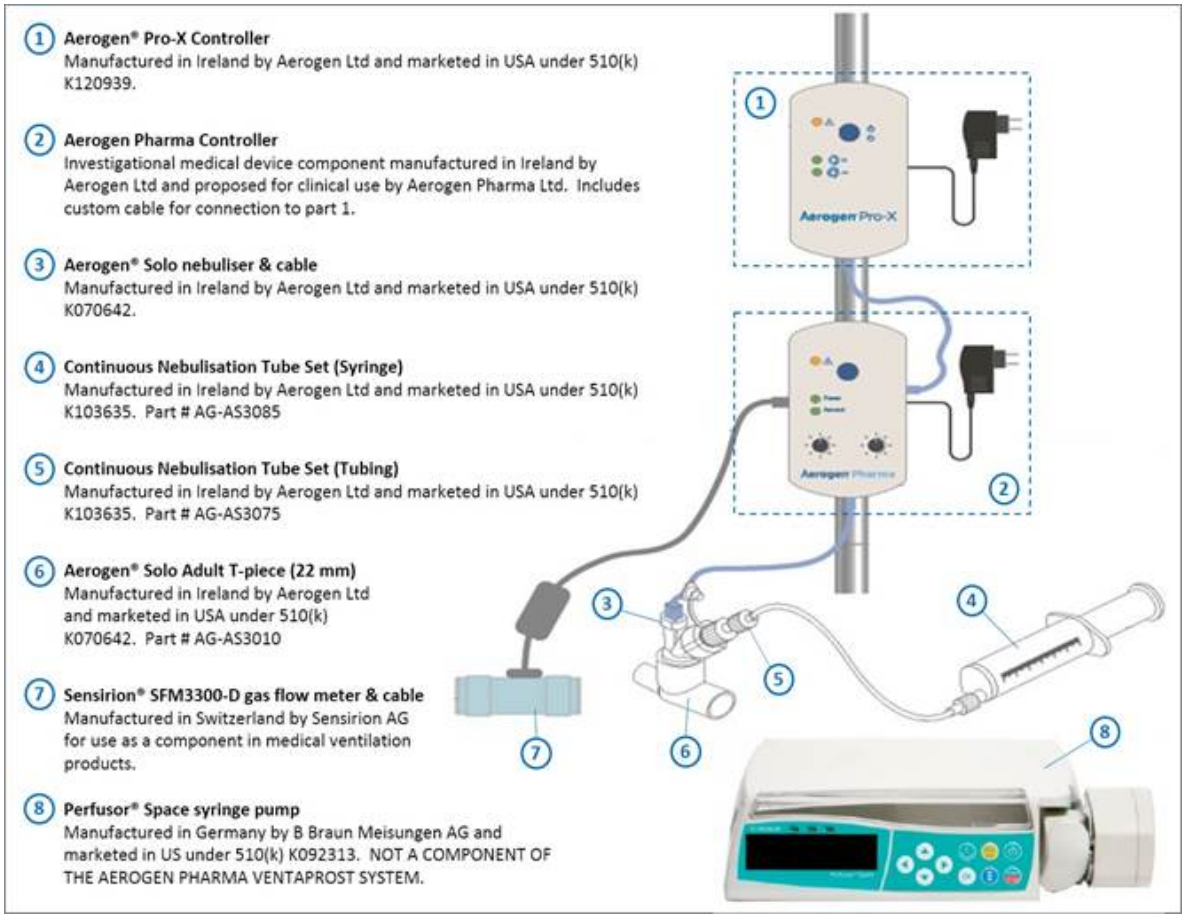
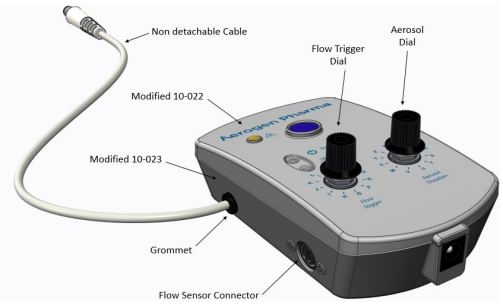


Figure 1: Drug Delivery System

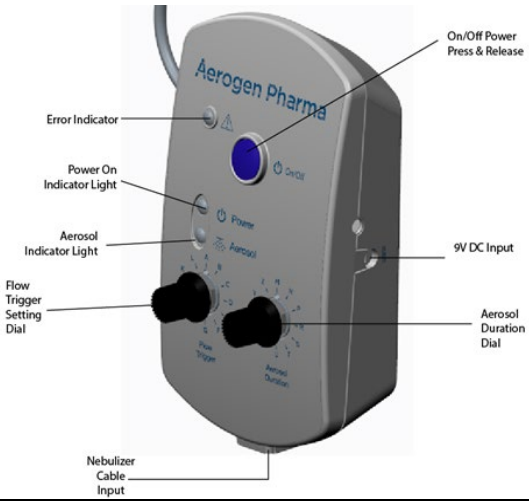
The Aerogen Pro-X (item #1, Figure 1), Aerogen Solo (item #3, Figure 1) are mounted on an I.V. pole at the patient's bedside. The two controllers and Aerogen CNTS (items #4 and 5, Figure 1) are routinely used as a system within their intended use. The sensor and nebulizer are connected into specific locations of the inspiratory limb of the ventilator pre- and post the humidifier, respectively (see Figure 2). The addition of the AP Controller and an off-the shelf Sensirion flow sensor enables the VentaProst system to synchronize aerosol delivery with the inspiratory cycle of the ventilator (Figures 1 and 2).

Figure 2 illustrates the AP Controller, which is similar to the commercially available Aerogen Pro-X controller in form, size, weight and materials used for the upper and lower shells. The AP Controller uses the same AC/DC adapter and cable as used in the commercial Aerogen Pro-X controller. The packaging used for the AP Controller is same as packaging validated by Aerogen Ltd. for the commercially available Aerogen Pro-X system. Functionality of the AP Controller was tested in design verification studies (IND129777). Two dials (Figure 2) are used to: (1) set the flow threshold for nebulization triggering during the inspiratory cycle of the ventilator, accommodating initial ventilator baseline bias flows, and (2) set the duration of nebulization during the inspiratory cycle (a detailed description of the mechanism of action of the AP Controller is presented in IND129777).

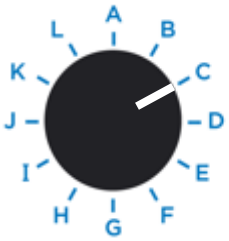
A. Diagram of Aerogen Pharma Controller (left side view)



B. Diagram of Aerogen Pharma Controller (right side view)

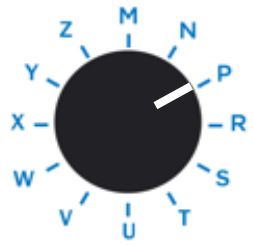


C. Flow Trigger Dial settings



A	2.5slm
B	4.0slm
C	5.5slm
D	7.0slm
E	8.5slm
F	10.0slm
G	11.5slm
H	13.0slm
I	14.5slm
J	16.0slm
K	17.5slm
L	19.0slm

D. Aerosol Duration Dial settings



M	0.3sec
N	0.4sec
P	0.5sec
R	0.6sec
S	0.7sec
T	0.8sec
U	0.9sec
V	1.0sec
W	1.1sec
X	1.2sec
Y	1.3sec
Z	1.4sec

Figure 2: Aerogen Pharma Controllers

Prior to VentaProst administration, the study medication will be reconstituted in the recommended diluent buffer and placed into two 60 mL CNTS syringes per the VPCOV Pharmacy Manual. These syringes should be protected from light. The user will attach the syringe to the CNTS tubing and prime the tube set so that the formulation reaches the Aerogen Solo, producing aerosol generation. The CNTS syringe set will be placed in a B Braun Perfusor Space Infusion syringe pump. The 15-mm T-Piece with nebulizer is placed between the ventilator circuit and the ETT (Figure 2). The user will select the pump rate to deliver the recommended dose based on the ideal body weight in kilograms (kg) dispensed to achieve the dose rate in ng/kg/min. The corresponding pump flow rate in mL/hour will be calculated based on initial dose of Flolan in ng/kg/min. The user will be able to adjust this recommended dose up or down (per protocol) by changing pump rate prior to selecting dose and initiating delivery. The selected dose will then be dispensed by the pump to the receiving surface of the mesh, resulting in generation of an aerosol with a volume median diameter in the range of 2 to 5 µm. The Aerogen Pharma Controller monitors the patient's breathing pattern and user adjusts the knob (on left) to initiate aerosol generation at the beginning of the breathing cycle. The knob on right sets the duration of aerosol generation within each breath.

The VentaProst device is designed to be compatible with standard intensive care unit

(ICU) equipment. The following site-specific equipment will be needed to deliver the therapy: B.Braun syringe pump, ventilator, endotracheal tube (ETT), humidifier, ventilator circuit. This equipment is standard for critical care medicine.

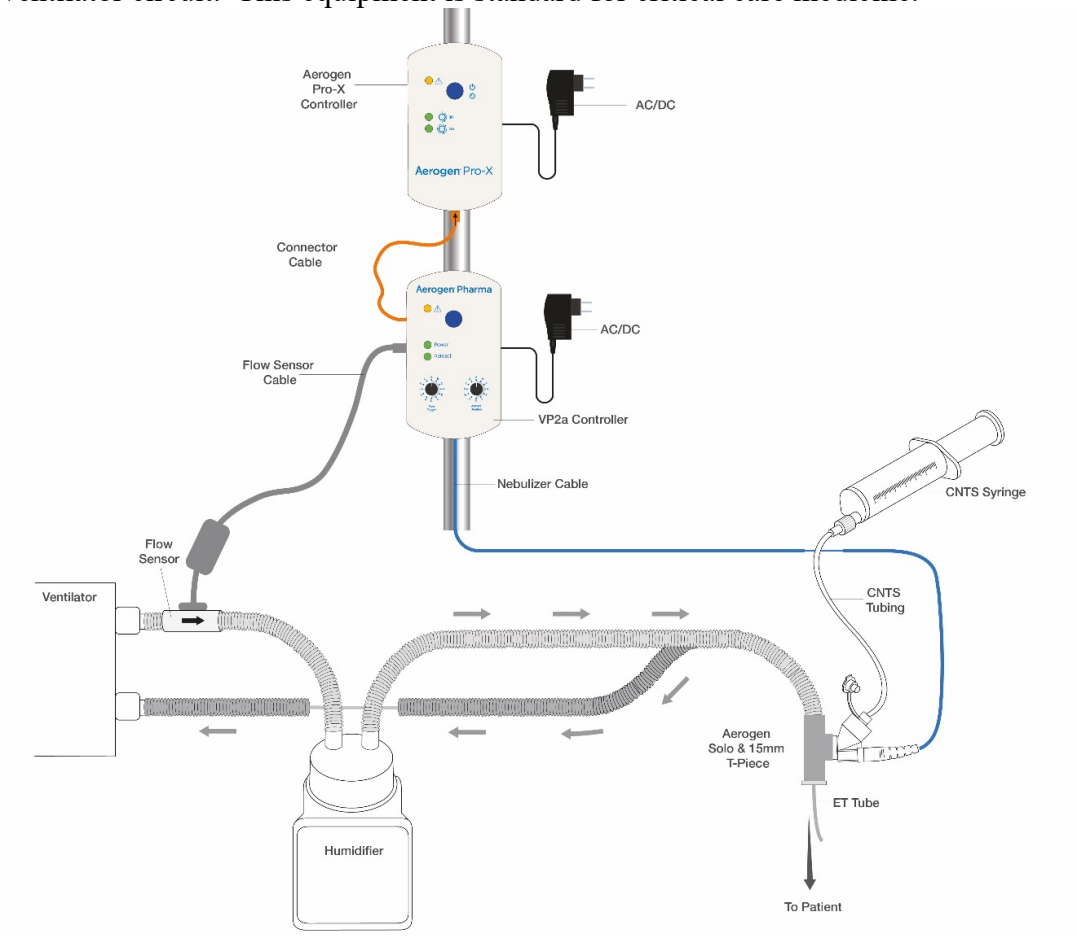


Figure 3 - VentaProst Device Placement in the Gas Pathway

5.4.2 Ventilator Settings

The device is designed for use with standard adult ventilator settings. An intermittent positive pressure ventilatory mode (i.e., not constant positive airway pressure [CPAP] or t-piece) is required to activate the device to deliver aerosol during the inspiration phase. A Heat-Moisture Exchanger (HME) may be used in the device circuit.

The site will utilize OSU's Standard of Care (SOC) mechanical ventilation guidelines for care of patients for COVID-19 with ARDS. The following ventilator parameters will be assessed daily while on VentaProst: Ventilator type, Mode, FiO_2, Inspiratory Time, Mean Airway Pressure, Peak Inspiratory Pressure, Positive End Expiratory Pressure, Respiratory Rate and Tidal Volume.

5.4.3 Device Supply

All device supplies will be provided by Aerogen Pharma Limited. The serial numbers for the controllers, flow sensor, and nebulizer will also be recorded in an IP accountability dispensing log.

Used and unused devices will be inventoried and returned to the Sponsor or Sponsor's designee.

5.4.4 Device Replacement

Devices may be replaced at any time if there a suspicion of malfunction, but must be replaced if:

- The investigator suspects that, due to device malfunction, less than 90% of the total dose of study medication is being delivered. Reduced doses must be estimated and recorded in the patient's medical record and source documentation.
- The investigator suspects the device is not performing optimally for any reason.

5.4.5 Device Malfunction or Failure

One device (Aerogen Pro-X controller, Aerogen Pharma Breath Controller, Flow Sensor, Solo nebulizer, CNTS syringe, and associated components) is expected to perform throughout the duration of study treatment. If the controllers, Flow Sensor, CNTS syringe, or the Solo nebulizer are not functioning optimally for any reason, instructions for trouble-shooting provided in the device instruction for use manual should be followed. If one or more devices need to be replaced, the reason should be documented in the patient's medical record, dispensing log, and Device Performance Issues Form. Additional devices are provided for this purpose. The unique serial numbers of the new components will be recorded in the patient's medical record, dispensing log, and the source documentation.

For device malfunction or complaints, complete the Device Performance Issues Log and submit to the Sponsor at Complaints@aerogenpharma.com within 48 hours. Failed devices will be set aside from the general supplies, inventoried and returned to the Sponsor or the Sponsor's designee.

5.5 Blinding

Since this is an open-label study, there will be no blinding of the study medication.

5.6 Prior and Concomitant Therapy

For patients who receive study medication, any medication (including over-the-counter [OTC] medications) or therapy administered to the patient during the course of the study (starting at Screening and 14 days prior) will be recorded on the Prior and Concomitant Therapy data collection forms. The Investigator will record any AE on the AE data collection forms for which a concomitant medication/therapy was administered.

5.6.1 Prohibited Concomitant Therapy

Other inhaled vasodilators besides VentaProst.

5.7 Investigational Product (IP) Supplies and Accountability

Investigational product supplies will not be sent to the Investigator(s) until the following documentation has been received by the Sponsor:

- Written proof of approval of the protocol and its informed consent forms (ICFs) by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for the institution where the study is to be conducted.
- An Investigator-signed and dated FDA Form 1572.
- A signed and dated curriculum vitae of the Principal Investigator including a copy of the Principal Investigator's current medical license (required in the US) or medical registration number on curriculum vitae.

The Investigator and study staff will be responsible for the accountability of all IP supplies (dispensing, inventory, and record keeping) following Aerogen Pharma instructions and adhere to Good Clinical Practice (GCP) guidelines as well as local and/or regional requirements.

Under no circumstances will the Investigator allow the IP to be used other than as directed by this protocol. IP will not be administered to any individual who is not enrolled into the study.

An accurate and timely record of the receipt of all IP; dispensing of IP to the patient; collection of unused IP; and subsequent return of unused IP to Aerogen Pharma must be maintained. This includes, but may not be limited to: (a) documentation of receipt of IP, (b) IP dispensing log, (c) IP accountability log, (d) all shipping service receipts, and (e) documentation of returned IP to the Sponsor. All forms will be provided by Aerogen Pharma. Any comparable forms that the investigational site wishes to use must be approved by Aerogen Pharma.

The supplies and inventory records must be made available, upon request, for inspection by the designated representative of Aerogen Pharma, a representative of the FDA, or a representative of a non-US health authority. All used and unused IP are to be returned to Aerogen Pharma at the conclusion of the study.

6. CRITERIA FOR EVALUATION

6.1 Primary Endpoint

1. Reduction of respiratory failure. Failure is defined by any one of the following:

    - Requires VV ECMO
    - Inability to extubate within 10 days or reintubation within < 24 hours
    - Change in S/F, oxygenation index and P/F ratio (≥15%) from baseline to 12 hours, Days 1, 2, 3, 4, 5, 6, 7, 8, 9 and Day 10 (or end of treatment)

or

1. Reduction of cardiac or circulatory failure. Failure is defined by any one of the following:

    - Need to begin inotropic 10% increase in current vasopressor therapy
    - Worsening hemodynamic parameters

- Cardiac troponin >20% from baseline
- BNP $\geq$ 15% of baseline
- Need for temporary mechanical circulatory support (IABP, Impella)
- Requires VA ECMO

6.2 Secondary Endpoints

1. Improvement in oxygenation defined as any one of the following:
    - Stabilization of PaO2/FIO2 >250
    - Improvement in FIO2 by 50% or improvements $\geq$15% in S/F, P/F ratio from baseline at 12 hours, Day 5 and Day 10 (or end of treatment)
2. Improved clinical outcomes defined as one of more of the following:
    - Time to extubation following the site's extubation protocol
    - Free from re-intubation
    - Reduction in ICU days
    - Reduction in the number of re-admissions to the ICU due to COVID-19 within 28 days
    - Reduction in total hospital days
    - Mortality [28 days] defined as Cardiopulmonary mortality or mortality from all causes
3. Safety and tolerability
    - Monitoring of adverse events (AEs), serious adverse events (SAEs), chest CT or Chest X-rays, vital signs, ventilatory/oxygenation parameters, and laboratory tests.

6.3 Exploratory endpoints will include (where available):

- Change in LDH
- Change in fibrinogen
- Change in WBC count including lymphocytes and neutrophil subsets
- Change in triglycerides
- Change in ferritin
- Change in CRP / ESR
- Change in IL-6
- Change in D-Dimer

6.4 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used and generally recognized as reliable, accurate, and relevant in studies of cardiac and respiratory function.

7. SAFETY ASSESSMENTS

Safety will be assessed through monitoring of adverse events (AEs) and serious adverse events (SAEs), laboratory tests, chest assessments (Chest CT or Chest X-ray), oxygenation/ventilatory parameters, and vital signs. Safety assessment frequency is shown in the Schedule of Assessments and Procedures.

7.1 General Safety Procedures

7.1.1 Vital Signs and Weight Measurements

Vital sign measurements, including systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) [beats per minute], respiratory rate (breaths per minute), and body temperature (in Celsius) will be obtained twice daily Days 1-10 or as clinically indicated. Weight (kg) will be obtained at the time of Screening and at Day 10 or end of VP treatment. Height will be obtained at the time of Screening. If unable to obtain height, the study staff will use the best reported historical height from patient or LAR.

7.1.2 Physical Examination

A physical examination will be conducted at the screening visit and will include assessments of general appearance; skin and lymphatics; eyes, ears, nose, throat; cardiovascular system; respiratory system; abdomen/gastrointestinal system; urological system; musculoskeletal and neurological systems. Other body systems may be examined as clinically indicated.

7.1.3 Laboratory Measurements

Clinical laboratory measurements to be performed are listed below. The Schedule of Assessments and Procedures shows the time points at which blood will be collected for clinical laboratory tests and pregnancy testing. The Baseline for laboratory tests is the Screening assessment.	
Category	Parameters
Hematology-CBC with diff	Hemoglobin, hematocrit, RBC, WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelets
Full Chemistry Panel	
Electrolytes	Sodium, potassium, chloride, bicarbonate, calcium
Liver function tests	AST, ALT, AP, total bilirubin
Renal function parameters	BUN, creatinine
Coagulation Studies	PT/PTT, D-Dimer
Other	Serum or urine pregnancy test, RT-PCR for COVID-19, ESR, Troponin, BNP, fibrinogen, ferritin, LDH, Triglycerides, D-Dimer, IL-6, and CRP

7.1.4 Chest Assessments

A Chest CT or Chest X-ray will be obtained at Screening and Day 5.

7.1.5 Time Prone Protocol

The time prone protocol is a standard of care in OSU's ICU. This will be in place for all days that patients are within the ICU.

7.2 Adverse Events

7.2.1 Definitions

Adverse events are any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. For the purposes of this study, this will include unanticipated medical events in the judgment of the investigator. ***A pre-existing condition*** or symptom is one that is present at the start of the study and is reported as part of the patient's medical history. A pre-existing condition or symptom should be reported as an AE only if its frequency, intensity or character worsens during study treatment.

All AEs that occur from the time of the first dose of study medication through the End of Study (Day 28) will be recorded and reported as Treatment-Emergent Adverse Events (TEAE). All AEs must be appropriately documented in the patient's medical chart/source documentation and on the DCFs. When known, investigators should report syndromes rather than list symptoms associated with the syndrome.

All AEs that are ongoing at the conclusion of the study should be followed until: a) resolution/stable sequelae; b) the Investigator determines that it is no longer clinically significant; or, c) the study patient is lost to follow-up. If no follow-up is provided, the Investigator must provide a written justification.

7.2.2 Grading of Adverse Events

The severity of each AE will be categorized using the following criteria:

- Grade 1 (Mild): usually transient; requires no special treatment and does not interfere with the patient's daily activities.
- Grade 2 (Moderate): produces a low level of inconvenience to the patient and may interfere with daily activities. These AEs are usually ameliorated by simple therapeutic measures.
- Grade 3 (Severe): interrupts daily activity and requires systemic drug therapy or other medical treatment.

7.2.3 Relationship to Study Medication/Study Device/Procedure

The Investigator must assess the relationship of each reported AE. The Investigator must make an assessment of the relationship of the AE to the study medication/study device/procedure using the following scale:

- Unrelated: The AE is definitely not or unlikely to be associated with study medication/study device/procedure and is judged due to causes other than the study medication/study device/procedure.
- Related: The AE is possibly or probably related with study medication/study device/procedure.

7.2.4 AE Outcomes

The following terms and definitions are used in assessing the final outcome of an AE:

- Recovered/Resolved - The patient has fully recovered, or by medical or surgical treatment, the condition has returned to the level observed at the first trial-related activity.
- Recovering/Resolving - The condition is improving and the patient is expected to recover from the event.
- Recovered/Resolved with sequelae - The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- Not recovered/Not resolved - The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known at the time of reporting.
- Fatal - This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as "recovered", "recovering", "recovered with sequelae" or "not recovered". An AE with fatal outcome must be reported as an SAE.

7.2.5 Laboratory Test and other Test Abnormalities as Adverse Events

A laboratory or other test (chest assessments, vital signs) abnormality should be reported as an AE if the Investigator considers the abnormality an AE or if the abnormality is associated with accompanying symptoms, requires medical/surgical intervention, leads to a change in study treatment, or results in discontinuation from the trial. When possible, syndromes not laboratory values, should be reported as AEs. For example, elevated hepatic transaminases associated with hepatitis should be reported as "hepatitis" and decreased hemoglobin and hematocrit requiring iron supplementation should be recorded as "anemia." Prior to reporting as an AE, abnormal tests should be repeated to verify the accuracy of the original result.

7.2.6 Serious Adverse Events

The Investigator is required to determine if each AE is a Serious Adverse Event (SAE). An SAE is any AE occurring after the first dose of study medication and results in any of the following outcomes:

- Death, or
- Is life-threatening, or
- Prolongation of existing hospitalization, or
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical

judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

In the event of death, the cause of death should be recorded as the SAE (death is an outcome, not the AE itself).

Any planned procedures that require admission to hospital as well as any planned elective procedures (e.g., angioplasty) are not considered SAEs (unless the underlying condition has worsened or the procedure results in a worsening of the patient's condition). In addition, pregnancy that occurs during the course of the study or absence of a treatment effect will also not be considered to be an SAE and will be collected on a separate CRF.

7.2.7 Reporting for SAEs (24 Hours)

Regardless of causality, an SAE must be followed clinically until resolution or stabilization.

All SAEs after the first dose of study medication through Day 28 of the study must be reported to the Sponsor or the Sponsor's representative within 24 hours of the investigational site's knowledge of the occurrence. The investigational site will email a Serious Adverse Event Report (SAER) to the Sponsor and the Medical Monitor. Investigational sites will be provided with SAER forms. The Medical Monitor will work closely with the Sponsor to properly assess and report the SAE.

The SAE information emailed to the Sponsor or the Sponsor's representative will include the following (as available):

- Patient Number, Investigator name, and Site Number
- SAE information: event term, onset date, severity, and causal relationship
- Basic demographic information (e.g., age, gender, weight)
- The outcomes attributable to the event (death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, other important medical event[s])
- A summary of relevant test results, pertinent laboratory data, and any other relevant medical history
- The first and last dates of study medication administration
- A statement whether study medication was discontinued or study medication administration schedule modified
- A statement whether event recurred after reintroduction of study medication if administration had been discontinued or withheld
- Supplemental anonymized information may include the following hospital records: laboratory results, radiology reports, progress notes, admission and emergency room notes, holding/observation notes, discharge summaries, autopsy reports, and death certificates

Supplemental information may be transmitted using a follow-up report and should not delay the initial report.

For regulatory purposes, initial reports of SAEs should be transmitted within the prescribed time frame as long as the following minimum information is available: patient number, suspect study medication, reporting source, and an event or outcome that can be identified as being both serious and unexpected for which the Investigator can make a relationship assessment.

7.3 Reporting of Pregnancy

Any pregnancy where the estimated date of conception occurs either prior to the End of Study must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study medication exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

An induced abortion or a spontaneous abortion is considered to be an SAE and should be reported in the same timeframe and in the same format as all other SAEs.

Pregnancies must be reported as soon as possible but no later than one business day by email.

All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but not later than 24 hours of the investigational site's knowledge of the outcome.

8. PHARMACOKINETIC ASSESSMENTS

Not applicable.

9. SCHEDULE OF ASSESSMENTS AND PROCEDURES

The assessments and procedures for this study are described in detail below and presented in the Schedule of Assessments and Procedures located behind the Synopsis.

9.1 Study Evaluation Timepoints

9.1.1 Screening (within 14 days prior to Baseline Day 1)

Potential study patients will be recruited by the study staff from patients. The following assessments will occur prior to study enrollment:

- Informed consent prior to any study procedures or assessments being performed.
- Demographic Information
- Medical History
- Physical Exam

- Prior Medication History
- Chest CT or Chest X-ray
- Inclusion/Exclusion Eligibility Assessment (including assessment of shortness of breath within the last 14 days)
- Serum/Urine Pregnancy Test (if woman of childbearing potential)
- Clinical Laboratory Sampling to include: Full Chemistry Panel including LFTs, CBC with Diff including neutrophils and lymphocytes, PT/PTT, Triglycerides, LDH, ferritin, fibrinogen, CRP, ESR, IL-6, troponin, BNP, D-Dimer, and RT-PCR for COVID-19
- Vital Signs
- Height & Weight (If height can't be obtained, use the best reported historical height)

9.1.2 Days 1-10 Treatment

9.1.2.1 Baseline-Day 1 (0 Hour)

- Continue evaluation eligibility by assessing Inclusion/Exclusion Criteria.
- Subjects will receive VentaProst, for a maximum of 10 days, as clinically indicated at the discretion of the Investigator. VentaProst dose will begin at 13.6 ng/kg/min and can be titrated up to 30.6 ng/kg/min or down to 3.4 ng/kg/min as clinically warranted. The B.Braun syringe pump will be set to the appropriate dose utilizing the subject's sex and height (ideal body weight).
- Vital signs will be assessed twice daily in AM and PM while on VentaProst. Efforts will be made to obtain vital signs at the same time each day. Vital signs include: temperature, pulse rate, respiration rate and blood pressure.
- Adverse Event/SAE assessment daily
- Concomitant medication evaluation daily
- Continuous pulse oximetry (SpO_2)
- Ventilatory parameters assessed twice daily while on VentaProst: Ventilator Type, Vent Mode, FiO_2, Inspiratory time, Mean Airway Pressure, Peak Inspiratory Pressure, Positive End Expiratory Pressure, Tidal Volume, and Respiratory Rate
- Time Prone Position-16 hours per day per OSU Protocol

9.1.2.2 Day 1-12 hours

- Clinical Laboratory Sampling to include: Full Chemistry Panel including LFTs, CBC with Diff including neutrophils and lymphocytes, PT/PTT, Triglycerides, LDH, ferritin, fibrinogen, CRP, ESR, IL-6, troponin, BNP, and D-Dimer.
- Continue to administer VentaProst if clinically indicated.

- Adverse Event/SAE assessment daily
- Concomitant medication evaluation daily
- Oxygenation measurement via continuous pulse oximetry (SpO_2)
- Ventilatory parameters assessed twice daily while on VP: Ventilator Type, Vent Mode, FiO_2, Inspiratory time, Mean Airway Pressure, Peak Inspiratory Pressure, Positive End Expiratory Pressure, Tidal Volume, and Respiratory Rate
- Vital signs will be assessed twice daily in AM and PM. Efforts will be made to obtain vital signs at the same time each day. Vital signs include: temperature, pulse rate, and blood pressure.
- Time Prone Position-16 hours per day per OSU Protocol

9.1.2.3 Days 2-10 (While on VentaProst)

- Continue to administer VentaProst if clinically indicated.
- Adverse Event/SAE assessment daily
- Concomitant medication evaluation daily
- Oxygenation measurement via continuous pulse oximetry (SpO_2)
- Ventilatory parameters assessed twice daily: Ventilator Type, Vent Mode, FiO_2, Inspiratory time, Mean Airway Pressure, Peak Inspiratory Pressure, Positive End Expiratory Pressure, Tidal Volume, and Respiratory Rate
- Vital signs will be assessed twice daily in AM and PM. Efforts will be made to obtain vital signs at the same time each day. Vital signs include: temperature, pulse rate, and blood pressure.
- Time Prone Position-16 hours per day per OSU Protocol
- Full Chemistry Panel including LFTs, CBC with Diff including neutrophils and lymphocytes, PT/PTT and RT-PCR for COVID-19. (Day 5 only)
- Chest CT or Chest X-ray (Day 5 only)
- Full Chemistry Panel including LFTs, CBC with Diff including neutrophils and lymphocytes, PT/PTT, Triglycerides, LDH, ferritin, fibrinogen, CRP, ESR, IL-6, troponin, BNP, D-Dimer, and RT-PCR for COVID-19 (Day 10 only).
- Obtain weight. (Day 10 only or at end of VP dosing)

9.1.2.4 Weaning

Patients will be weaned from VentaProst slowly due to concern that VentaProst is providing significant clinical benefit and to avoid a rebound effect. Doses will be

decreased in steps of 3.4 ng/kg/min increments with a minimum of 15 minutes between changes until VentaProst is discontinued.

9.1.3 Day 28/End of Study (EOS)

- Assess AEs/SAEs
- Assess Mortality
- Assess concomitant medications

9.2 Data Collection

Investigator or designee will enter the information required by the protocol onto source documents and enter data into data collection forms (DCFs) in an excel spreadsheet provided by Aerogen Pharma.

9.3 Clinical Data Management

Data from source documents will be verified against the DCF and any discrepancies will be clarified and resolved with study staff.

9.4 Database Quality Assurance

All databases will be remotely monitored by the Sponsor due to the COVID-19 pandemic. Should restrictions be lifted at OSU, an on-site visit may occur if all parties are in agreement.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Methods

A Statistical Analysis Plan will be not be developed as this is an exploratory trial. Any statistical evaluation will be handled internally by Aerogen Pharma or their designee.

10.2 Determination of Sample Size

The number of patients has been selected to enable an adequate clinical assessment of pharmacodynamics, safety, and tolerability parameters without presenting undue risk to a large number of patient's being exposed to this investigational product.

10.3 Analyses Sets

All patients who are enrolled in the study and who receive at least one dose of VentaProst will be included in the intent-to-treat (ITT) analyses of pharmacodynamic and safety data. All available data will be used and missing data will not be estimated or carried forward in any statistical summary or analyses.

Descriptive summary statistics include the number of patients, mean, median, percent coefficient of variation (% CV) (if required), standard deviation, and minimum and maximum values (quantitative variables) or the number of patients and percentages by category (qualitative variables). Changes will be assessed as the difference between baseline measurements and the appropriate post-dose measurements unless otherwise

specified. Mean differences between active and historical control groups (when available) will be assessed and significance will be determined on the basis of a 95% CI. Individual patient listings of data will also be provided to allow for review of all pharmacodynamic, safety, and tolerability parameters.

10.4 Demographic and Other Baseline Characteristics

Continuous demographic and other baseline characteristics (such as age, weight, and height) will be summarized using n, mean, SD, median, minimum, and maximum. Qualitative characteristics (such as gender and race) will be summarized by counts and percentages.

10.5 Criteria for Evaluation

10.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint:

1. Reduction of respiratory failure. Failure is defined by any one of the following:

    - Requires VV ECMO
    - Inability to extubate patient within 10 days or reintubation within <24 hours
    - Change in S/F, oxygenation index and P/F ratio (≥15%) from baseline to 12 hours, Days 1, 2, 3, 4, 5, 6, 7, 8, 9 and Day 10 (or end of treatment)

or

2. Reduction of cardiac or circulatory failure. Failure is defined by any one of the following:

    - Need to begin inotropic or 10% increase in current vasopressor therapy
    - Worsening hemodynamic parameters
    - Cardiac troponin >20 % from baseline
    - BNP ≥ 15% of baseline
    - Need for temporary mechanical circulatory support (IABP, Impella)
    - Requires VA ECMO

10.5.2 Secondary Efficacy Endpoints

Key secondary endpoints include:

1. Improvement in oxygenation defined as any one of the following:
    - Stabilization of PaO2/FIO2 >250
    - Improvement in FIO2 by 50% or improvements ≥15% in S/F, P/F ratio from baseline at 12 hours, Day 5 and Day 10 (or end of treatment)
2. Improved clinical outcomes defined as one of more of the following:

- Time to extubation following the site's extubation protocol
- Free from reintubation
- Reduction in ICU days
- Reduction in the number of re-admissions to the ICU due to COVID-19 within 28 days
- Reduction in total hospital days
- Mortality [28 days] defined as Cardiopulmonary mortality or mortality from all causes

3. Safety
   - Monitoring of adverse events (AEs), serious adverse events (SAEs), chest CT or Chest X-rays, vital signs, ventilatory/oxygenation parameters, and laboratory tests.

10.5.3 Key Exploratory Endpoints include:

- Change in LDH
- Change in fibrinogen
- Change in WBC count including lymphocytes and neutrophil subsets
- Change in triglycerides
- Change in ferritin
- Change in CRP / ESR
- Change in IL-6
- Change in D-Dimer

10.6 Extent of Exposure

Exposure data will be summarized by using frequencies and percentages.

10.7 Safety Analyses

Safety measurements include AE/SAEs, vital signs, chest assessments (Chest CT or Chest X-ray), laboratory tests, and oxygenation/ventilatory parameters. Safety data will be summarized by using frequencies and incidence rates.

10.7.1 Adverse Events

AEs will be classified into standardized medical terminology from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be presented by preferred term nested within System Organ Class. Verbatim description and all MedDRA level terms, including the lower level terms, for all AEs will be contained in the data listings of the clinical study report (CSR).

AEs will be summarized by presenting the incidence of AEs. Although a MedDRA term may be reported more than once for a patient, that patient will be counted only one time in the incidence count for that MedDRA term.

Treatment-emergent adverse events (TEAEs) will be analyzed. AEs that are not treatment-emergent will be listed. A TEAE is defined as

- AEs that emerge during treatment, having been absent at pretreatment, or
- Reemerge during treatment, having been present at pretreatment but stopped prior to treatment, or
- Worsen in severity or frequency during treatment relative to the pretreatment state, when the AE is continuous.

10.7.2 Laboratory Values

Clinical laboratory results post-Baseline will be evaluated for markedly abnormal values. For the incidence of markedly abnormal laboratory values, each patient may be counted once in the laboratory parameter value high and in the laboratory parameter low categories as applicable. Descriptive summary statistics (e.g. mean, SD, median, minimum, maximum) for laboratory values and changes from baseline will be evaluated.

10.7.3 Vital Signs

Vital sign values will be evaluated on an individual basis by patient. Abnormal vital sign values will be identified as those outside (above or below) the reference range. Descriptive summary statistics (e.g., mean, SD, median, minimum, maximum) for vital sign parameters and changes from Baseline will be evaluated.

10.8 The Procedure for Revising the Statistical Analysis Plan

Not Applicable.

11. ADMINISTRATIVE PROCEDURES AND INSTRUCTIONS

11.1 Ethics

11.1.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an IRB or IEC constituted and functioning in accordance with International Conference on Harmonization (ICH) E6, Section 3, and any local regulations, i.e., Federal Regulations, Title 21 Code of Federal Regulations (CFR) Part 56. Any protocol amendment and/or revision to the ICF will be resubmitted to the IRB/IEC for review and approval (except for changes involving only logistical or administrative aspects of the study (e.g., change in CRA[s], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

A signed letter of study approval from the IRB/IEC Chairman must be sent to the Principal Investigator with a copy to the Sponsor prior to study start and the release of

any investigational products to the site by the Sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the Investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the Sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the Investigator or Sponsor, depending on local regulatory obligations. If the Investigator is required to report to the IRB/IEC, he/she will forward a copy to the Sponsor at the time of each periodic report. The Investigator or the Sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable AEs per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the Investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

11.1.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating practices of Aerogen Pharma (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- ICH - E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonization of Pharmaceuticals for Human Use.
- US CFR dealing with clinical studies (21 CFR, including parts 50 and 56 concerning Informed Patient Consent and IRB regulations).

11.1.3 Patient Information and Informed Consent

As part of administering the informed consent document, the Investigator must explain to each patient or their legally authorized representative (LAR), the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, and currently available alternative treatments. Each patient must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The patient or their LAR should understand the statement before signing and dating it and will be given a copy of the signed document. The patient or their LAR will be asked to sign an informed consent prior to any study-specific procedures being performed. No patient can enter the study before his/her informed consent has been obtained. Due to the COVID-19 pandemic and restrictions on hospital visitors, informed consent may be obtained via telephone or video conference call if the patient is incapacitated or sedated due to the severity of their illness. A witness for the study team should be present when a call or video conference is occurring with the patient's LAR. This process should be carefully documented in the subject's medical records.

An unsigned copy of an IRB/IEC and Sponsor-approved written informed consent must be prepared in accordance with ICH E 6, Section 4, and all applicable local regulations,

i.e., Federal Regulations, Title 21, CFR Part 50, and provided to the Sponsor. Each patient or their LAR must sign an approved informed consent prior to study participation. The form must be signed and dated by the appropriate parties. The original signed ICF for each patient will be verified by the Sponsor and kept in the study center's investigational site files.

The patient should be informed in a timely manner if new information becomes available that might be relevant to the patient's willingness to continue participation in the trial. The communication of this information should be documented.

11.2 Administrative Procedures

11.2.1 Changes to the Protocol

There are to be no changes to the protocol without written approval from the Sponsor. Protocols will be followed as written.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of patients, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRBs/IECs of all investigational sites and, as required, by the regulatory authority. These requirements should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all patients included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary for safety reasons, the Medical Monitor must be notified promptly and the IRB/IEC for the site must be informed as soon as possible.

Changes affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval, but the IRB/IEC must be kept informed of such changes. In these cases, the Sponsor will send a letter to the site for forwarding on to the IRB/IEC detailing such changes.

11.2.2 Adherence to the Protocol

The Investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.2.3 Monitoring Procedures

The Sponsor or Sponsor's representative will maintain contact with the Investigator and designated staff by telephone, letter, and/or email between study visits. Monitoring visits to each investigational site will be conducted by the sponsor either remotely or in person.

In accordance with ICH E6, Section 6.10, source documents include, but are not limited to the following:

- Clinic, office, hospital charts.
- Copies or transcribed health care provider notes which have been certified for accuracy after production.

- Recorded data from automated instruments such as mechanical ventilators, x-rays, and other imaging reports, e.g., sonograms, computed tomography scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, electroencephalographs, polysomnography, pulmonary function tests (regardless of how these images are stored, including microfiche and photographic negatives).
- Records of telephone contacts.
- Diaries or evaluation checklists.
- Investigational product distribution and accountability logs maintained in pharmacies or by research personnel.
- Laboratory results and other laboratory test outputs, e.g., serum pregnancy test result documentation.
- Correspondence regarding a study patient's treatment between physicians or memoranda sent to the IRBs/IECs.
- CRF components (e.g., questionnaires) that are completed directly by patients and serve as their own source.

11.2.4 Recording of Data

In order to provide the Sponsor with accurate, complete, and legible records following criteria are to be maintained. The Investigator will enter the information required by the protocol onto the data collection forms (DCFs) provided by the sponsor as agreed upon with the research staff.

11.2.5 Data Storage and Retention of Records

The circumstances of completion or termination of the study notwithstanding, the Investigator has the responsibility to retain all study documents, including but not limited to the protocol, copies of data collection forms (DCFs) , Investigator's Brochure, regulatory agency registration documents, e.g., FDA 1572 form, ICFs, and IRB/IEC correspondence. The investigational site should plan on retaining study documents as follows:

- For at least two years following the date a marketing application is approved for the investigational product for the indication for which it is being investigated, or
- Until two years after the investigation is formally discontinued and no application is to be filed or if the application is not approved.

It is requested that at the completion of the required retention period, or should the Investigator retire or relocate, the Investigator contacts the Sponsor, allowing the Sponsor the option of permanently retaining the study records.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Data will be coded (de-identified), stored in a secure electronic database during and after

the study, and will not be shared with unauthorized persons. The principal investigator and co-investigator will have access to the data to review and analyze the data, as described in this protocol. For the protection and privacy of the patients, no identifying information will be released.

Data will be retained and possibly used in the future for further analysis. All identifiers will be removed and not be shared at any time.

11.2.6 Handling of Investigational Product

All IP will be procured by OSU on behalf of Aerogen Pharma and maintained within the site's Investigational Pharmacy. It will be inventoried and stored according to their protocols and procedures. Since Flolan will be procured by OSU, the drug should not be dispensed to patients in the VentaProst COVID trial (APC-VPCOV-CLN-001) until a favorable IRB approval has been obtained by the OSU IRB and a study initiation visit has been conducted by the Sponsor. Investigation product supplies must be kept in an appropriate secure area (e.g., locked cabinet) and stored according to the conditions specified on the investigational product labels. The Investigator (or designated pharmacist) must maintain an accurate record of the shipment and dispensing of the IP in an IP accountability log, a copy of which must be given to the Sponsor at the end of the study. An accurate record of the date and amount of IP dispensed to each patient must be available for inspection at any time. The assigned sponsor representative will review these documents along with all other study conduct documents at an appropriate interval of visit to the investigational site once IP has been received by the investigational site. Due to COVID-19 a physical inventory of IP (drug and device supplies) may not be possible. If at all possible, an inventory of supplies should be conducted via video conferencing. If video conferencing is not possible, study staff will inventory supplies and provide documentation to Aerogen Pharma.

All IP supplies are to be used only for this protocol and not for any other purpose. The Investigator (or designated pharmacist) must not destroy any IP product labels or any partly used or unused IP supply without Sponsor authorization. At the conclusion of the study and as appropriate during the course of the study, the Investigator (or designated pharmacist) will return or properly dispose of all used and unused IP. Unused investigational device components will be returned to Aerogen Pharma at the conclusion of the study.

11.2.7 Publication of Results

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each Investigator and Aerogen Pharma, as appropriate.

11.2.8 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the course of this study will be kept confidential by the Investigator, the Investigator's staff, and IRB/IEC and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study without the written consent of the Sponsor.

No data collected as part of this study will be utilized in any written work, including publications, without the written consent of Sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in the Confidentiality Agreement between the Sponsor and the Investigator. All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Confidentiality Agreement between the Investigator and Sponsor (provided by the Sponsor).

11.2.9 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time.

The Investigator reserves the right to discontinue the study should his/her judgment so dictate. If the Investigator terminates or suspends a trial without prior agreement of the Sponsor, the Investigator should inform the Institution where applicable, and the Investigator/Institution should promptly inform the Sponsor and the IRB/IEC and should provide the Sponsor and the IRB/IEC a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.2.10 Patient Insurance and Indemnity

The Sponsor will provide the insurance in accordance with local guidelines and requirements as a minimum for the patients participating in this study.

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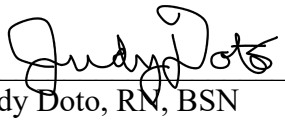
PROTOCOL TITLE	**TITLE: DOUBLE-BLIND, PLACEBO CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF VENTAPROST (INHALED EPOPROSTENOL DELIVERED VIA DEDICATED DELIVERY SYSTEM) IN SUBJECTS WITH COVID-19 REQUIRING MECHANICAL VENTILATION**
PROTOCOL NUMBER	APC-VPCOV-CLN-001
INVESTIGATIONAL PRODUCT	VentaProst™
INDICATION	Reduction of respiratory, cardiac or circulatory failure in patients with COVID-19
PHASE	Phase 2a
SPONSOR	Aerogen Pharma Limited 1660 S Amphlett Boulevard, Suite 360 San Mateo, CA 94402 United States
MEDICAL MONITOR	Matthew Exline, MD
AMENDMENT #1 APPROVAL DATE	21 July 2020
GCP STATEMENT	This study is to be performed in full compliance with International Conference on Harmonization (ICH) and all applicable local Good Clinical Practices (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
CONFIDENTIALITY STATEMENT	This document is confidential as it contains proprietary information of Aerogen Pharma. Any viewing or disclosure of such information that is not authorized in writing by the Aerogen Pharma is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

SPONSOR PROTOCOL APPROVAL PAGE

PROTOCOL TITLE	**A DOUBLE-BLIND, PLACEBO CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF VENTAPROST (INHALED EPOPROSTENOL DELIVERED VIA DEDICATED DELIVERY SYSTEM) IN SUBJECTS WITH COVID-19 REQUIRING MECHANICAL VENTILATION**
PROTOCOL NUMBER	**APC-VPCOV-CLN-001**
AMENDMENT #1 APPROVAL DATE	**21 July 2020**



21 July 2020

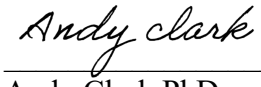
Judy Doto, RN, BSN — Date
Head of Clinical Operations
Aerogen Pharma

21 JUL 2020

Jim Fink PhD, RRT, FCCP — Date
Chief Scientific Officer
Aerogen Pharma

21 JUL 2020

Plamena Entcheva-Dimitrov, PhD, RAC — Date
Head of Regulatory and Medical Affairs
Aerogen Pharma



21 July 2020

Andy Clark PhD — Date
Vice President and General Manager
Aerogen Pharma

INVESTIGATOR'S SIGNATURE PAGE

PROTOCOL TITLE	**A DOUBLE-BLIND, PLACEBO CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF VENTAPROST (INHALED EPOPROSTENOL DELIVERED VIA DEDICATED DELIVERY SYSTEM) IN SUBJECTS WITH COVID-19 REQUIRING MECHANICAL VENTILATION**
PROTOCOL NUMBER	**APC-VPCOV-CLN-001**
AMENDMENT #1 APPROVAL DATE	**21July 2020**

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with ICH-GCPs and all applicable local guidelines.

_____

Principal Investigator (printed/typed)

_____

Principal Investigator Signature Date

1. CLINICAL PROTOCOL SYNOPSIS

Sponsor	Aerogen Pharma
Protocol No.	APC-VPCOV-CLN-001
Title of Study	Double-blind, placebo controlled study to assess the efficacy and safety of VentaProst (Inhaled epoprostenol delivered via dedicated delivery system) in subjects with COVID-19 requiring mechanical ventilation.
Study Centers	One clinical site in the US
Phase	Phase 2a
Objectives	**Primary Objective:** The primary objective of this study is the reduction of respiratory, cardiac or circulatory failure in patients with confirmed COVID-19. **Secondary Objectives:** The secondary objective in this study is to evaluate the effects of VentaProst on improvement in oxygenation and improvement in clinical outcomes. The study will also evaluate the effects of VentaProst on inflammatory parameters in subjects with confirmed COVID-19.
Study Design	This is a double-blind, placebo controlled study of VentaProst (Active) as compared to placebo (Control). Active is inhaled epoprostenol administered via the VentaProst delivery system in 10 COVID-19 positive patients. Control is inhaled 0.9% sodium chloride solution administered via the VentaProst delivery system in 10 COVID-19 positive patients. Throughout the remainder of the protocol both Active and Control will be referred to as "study drug". This study will evaluate the potential therapeutic benefit of VentaProst in treating patients with COVID-19 who require mechanical ventilation and are at risk for the progression of respiratory and/ or cardiac/circulatory failure. This study will assess the efficacy and safety of VentaProst at an initial dose of 13.6 ng/kg/min (A range from 3.4-30.6 ng/kg/min may be administered as clinically required for a maximum of 10 days at the discretion of the Investigator. Patients will be followed through Day 28 to assess clinical outcomes. Patients will be consented and randomized to either the Active or Control group within 24 hours of being placed on a mechanical ventilator. Patients will be administered study drug using the VentaProst delivery system which allows up and down titration of study drug to achieve hemodynamic and oxygenation stability. The starting dose of study drug will be initiated at 13.6 ng/kg/min. Based on hemodynamic and oxygenation parameters, the dose of study drug can be increased in 3.4 ng/kg/min increments up to a maximum of 30.6 ng/kg/min or down to a minimum of 3.4 ng/kg/min. Study drug will be administered based on the pump rate calculated for active treatment in mL/hr. The titration table below (Table 1) shows the typical up and down titration steps for study drug.

<table>
<tr><td></td><td>

Table 1: Overview of Titration and Weaning Guidelines

Up titration Guideline*	Downward Titration / Weaning Guideline**
Start Dose: 13.6 ng/kg/min 1st Step Up Dose (17.0) 2nd Step Up Dose (20.4) 3rd Step Up Dose (23.8) 4th Step Up Dose (27.2) 5th Step Up Dose (30.6)	Start Dose: 13.6 ng/kg/min 1st Step Down dose (10.2) 2nd Step Down Dose (6.8) 3rd Step Down dose (3.4)

* The study drug will be administered based on the pump rate calculated for active treatment in mL/hr.**If the patient has been up-titrated weaning should occur from that level in 3.4 ng/kg/min decrements.

Patients will be weaned from study drug slowly to avoid rebound vasoconstriction. During weaning, doses will be decreased in steps of 3.4 ng/kg/min increments, with a minimum of 15 minutes between changes. The weaning process should occur in isolation to other treatment changes (no changes in inotropes, vasopressors, or vasodilators) whenever possible. Patients will be observed closely before, during, and after dose changes. In the event patients demonstrate signs of hemodynamic instability or a decrease in oxygenation indicated by pulse oximetry during downward titration, the dose will be returned to its previous level. Once patients have been stable for at least 15 minutes, repeat attempts at dose reduction may be undertaken. The process will continue until patients are fully weaned. Patients will be monitored for safety and efficacy throughout study drug administration.
</td></tr>
<tr><td>Number/Type of Patients</td><td>

Approximately 20 COVID-19 positive patients requiring mechanical ventilation will be enrolled in this study.

Patients will be randomized to either VentaProst Active (aerosolized epoprostenol administered via the VentaProst delivery system) or VentaProst Control (aerosolized 0.9% sodium chloride solution administered via the VentaProst delivery system).
</td></tr>
<tr><td>Inclusion Criteria</td><td>

Patients are eligible for this study if they meet all of the following criteria:

1. Women and Men Age ≥18 years old (no upper limit)
2. Confirmed COVID-19 positive by RT-PCR test
3. Patients who require invasive mechanical ventilation.
4. Enrolled into study within 24 hours of being placed on mechanical ventilation
5. Consent or professional consent obtained
6. Duration of shortness of breath must be within the previous 14 days.
7. Female subjects of childbearing potential must have a negative pre-treatment pregnancy test (serum or urine).
8. Received or currently receiving dexamethasone for the treatment of COVID.
9. Willing and able to comply with treatment schedule and follow-up.
</td></tr>
</table>

Exclusion Criteria	Patients are **NOT** eligible for this study if they meet any of the following criteria: 1. Patients on ECMO support. 2. Patients receiving another inhalation research medication or inhaled nitric oxide. 3. Not expected to survive for 48 hours. 4. Pregnant (positive pregnancy test in a pre-dose examination) or breastfeeding 5. Open tracheostomy. 6. Clinical contra-indication, as deemed by the attending physician. 7. Allergy to Epoprostenol and its diluent 8. Using inhaled vasodilators at baseline. 9. Patients who are hemodynamically unstable as determined by investigator 10. Patients with significant hemoptysis as determined by investigator
Study Treatment(s)	Patients will receive study drug via mechanical ventilator, starting at 13.6 ng/kg/min. If determined by the treating physician, study drug can be up titrated in 3.4 ng/kg/min increments to a maximum of 30.6 ng/kg/min or down to a minimum of 3.4 ng/kg/min. At the Investigator's discretion, the patient will be weaned off the drug in 3.4 ng/kg/min increments. Study drug will be administered based on the pump rate calculated for active treatment in mL/hr. Study drug can be administered up to 10 days.
Duration of Treatment	The duration of study participation for each patient is as follows: • Screening: up to 14 days • Treatment: up to 10 days • Follow up: 28 days
Criteria for Evaluation	<u>Primary Endpoint</u> 1. Reduction of respiratory failure. Failure is defined by any one of the following: • Requires VV ECMO • Inability to extubate patient within 10 days or reintubation within < 24 hours • Change in S/F, oxygenation index and P/F ratio (≥15%) from baseline to 12 hours, Days 1, 2, 3, 4, 5, 6, 7, 8, 9 and Day 10 (or end of treatment) **or** 2. Reduction of cardiac or circulatory failure. Failure is defined by any one of the following: • Need to begin inotropic therapy or 10% increase in current vasopressor therapy • Worsening hemodynamic parameters • Cardiac troponin > 20% from baseline • BNP ≥ 15% of baseline • Need for temporary mechanical circulatory support (IABP, Impella) • Requires VA ECMO <u>Secondary Endpoints:</u> 1. Improvement in oxygenation defined as any one of the following: • Stabilization of PaO2/FIO2 >250 • Improvement in FIO2 by 50% or improvements <u>≥</u>15% in S/F, P/F ratio from baseline at 12 hours, Day 5 and Day 10 (or end of treatment)

	2. Improved clinical outcomes defined as one of more of the following: • Shorter time to extubation following the site's extubation protocol • Free from reintubation • Reduction in ICU days • Reduction in the number of re-admissions to the ICU due to COVID-19 within 28 days. • Reduction in hospital days Mortality (28 Days) defined as Cardiopulmonary mortality or mortality from all causes. 3. Safety and tolerability: • Monitoring of adverse events (AEs), serious adverse events (SAEs), chest CT or Chest X-rays, vital signs, ventilatory and oxygenation parameters, and laboratory tests. **Exploratory endpoints will include (where available):** 1. Change in LDH 2. Change in fibrinogen 3. Change in WBC count including lymphocytes and neutrophil subsets 4. Change in triglycerides 5. Change in ferritin 6. Change in CRP / ESR 7. Change in IL-6 8. Change in D-Dimer Changes in these parameters will be assessed for each patient from baseline to end of study as well as changes between the active and control groups.
Ventilatory Parameters	<u>OSU SOC:</u> Ventilator Type (GE) Parameters to monitor are: 1. Ventilator Mode 2. FiO_2 3. Inspiratory Time 4. Mean Airway Pressure 5. Peak Inspiratory Pressure 6. Positive End Expiratory Pressure 7. Respiratory Rate 8. Tidal Volume
Criteria for Stopping VentaProst Treatment	**<u>Individual patients stopping criteria:</u>** At any time during study drug administration, patients may be removed from study treatment and placed on standard of care (SoC) therapy if they meet one or more of the following pre-defined criteria leading to a deterioration in their condition: • Severe hypotension as evidenced by a systolic BP < 90 mmHg or MAP < 60 mmHG for >2 hours from the start of VentaProst • Need for VV ECMO • Need to increase existing vasopressor therapy by more than 25%

	• Worsening in oxygenation, ventilatory, or hemodynamic parameters that in the opinion of the investigator the patient should be removed from study treatment • Massive hemoptysis thought to be clinically significant and not related to endotracheal tube trauma • Pulmonary edema • If a clinically inadequate response to treatment is observed **Study stopping criteria:** If 3 patients are removed from the study for any of the above conditions, the study will stop further enrollment and an investigation will be conducted to determine the cause of the events. An independent safety evaluation will also be conducted. If it is suspected that the investigational product has caused the events, the study will be terminated. **Independent Safety Evaluation:** Independent safety evaluation will be conducted by a licensed physician who is not involved in the VentaProst COVID-19 clinical study or the sponsoring organization.
Statistical Methods	All patients who are enrolled in the study and who receive at least one dose of study drug will be included in the intent-to-treat (ITT) analyses of pharmacodynamic and safety data. All available data will be used and missing data will not be estimated or carried forward in any statistical summary or analyses. Descriptive summary statistics include the number of patients, mean, median, percent coefficient of variation (% CV) (if required), standard deviation, and minimum and maximum values (quantitative variables) or the number of patients and percentages by category (qualitative variables). Changes will be assessed as the difference between baseline measurements and the appropriate post-dose measurements unless otherwise specified. Mean differences between active and historical control groups will be assessed and significance will be determined on the basis of a 95% CI. No formal estimate of the sample size has been made. This is an exploratory study and the number of patients was selected to enable an adequate clinical assessment of pharmacodynamic, safety, and tolerability parameters without presenting undue risk to a large number of patients.
Efficacy Analysis	Efficacy will be secondarily determined by summarizing success or failure to meet any of the primary or secondary endpoints as compared to Control treatment.
Safety Analyses	Safety data will be summarized for both treatment groups including frequencies and incidence rates. Safety will be assessed through monitoring of adverse events (AEs), serious adverse events (SAEs), chest CTs or chest X-rays, laboratory tests, oxygenation and ventilatory parameters, and vital signs.

Table 2: Schedule of Assessments and Procedures

	Screening	VentaProst - Day 1		VentaProst Days 2-10									End of Study
Study Procedures	**Within 14 Days Prior to Baseline**	**Baseline - 0 Hr**	**12 hrs**	**D-2**	**D-3**	**D-4**	**D-5**	**D-6**	**D-7**	**D-8**	**D-9**	**D-10**	**Day 28 (+/- 2 days)**
Written Informed Consent	X												
Demographics	X												
Medical History	X												
Review Inclusion/Exclusion Eligibility Criteria	X	X											
Medication History/ Prior Meds	X												
Physical Examination	X												
Weight/Height[1]	X											X	
Randomization		X											
Chest CT Scan or CXR	X						X						
Clinical Laboratory Sampling[2]	X		X				X					X	
Pregnancy Test (Serum or Urine)	X												
RT-PCR + for COVID-19	X						X					X	
Administer VentaProst		X	X	X	X	X	X	X	X	X	X	X	
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	
Oxygenation Measurements[4]		X	X	X	X	X	X	X	X	X	X	X	
Ventilator Parameters[5]		X	X	X	X	X	X	X	X	X	X	X	
AE/SAE Monitoring		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X
Prone position		X	X	X	X	X	X	X	X	X	X	X	

[1] Height only performed at screening

[2] Clinical Labs include: Safety labs: CBC (lymphocyte and neutrophil counts), Full Chemistry Panel (including LFTs) and PT/PTT drawn Screening, Day 1-12 hours, Days 5 & 10. Triglycerides, LDH, ferritin, fibrinogen, CRP, ESR, IL-6, D-Dimer, troponin, BNP drawn at Screening, Day 1-12 hours and D-10.

[3] Vital signs: Prior to initiating VentaProst, Days 1-10 twice daily (morning and evening) at the same time to reduce exposure to Health Care Professionals to include; temperature, pulse rate, blood pressure.

[4] Continuous SpO2 via pulse oximetry

[5] Ventilator Parameters will be collected twice daily along with vital signs and include: Ventilator Type, Ventilator Mode, FiO_2, Inspiratory Time, Mean Airway Pressure, Peak Inspiratory Pressure, Positive End Expiratory Pressure, Tidal Volume and Respiratory Rate

[6] Time Prone Position – 16 hours per day per OSU protocol

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List of Figures and Tables

LIST OF ACRONYMS, ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
Active	Inhaled epoprostenol administered via the VentaProst delivery system
AE	Adverse |Event
ALI	Acute Lung Injury
ALT (SGPT)	Alanine Aminotransferase (serum glutamic pyruvic transaminase)
AP	Alkaline Phosphatase
ARDS	Acute Respiratory Distress Syndrome
AST (SGOT)	Aspartate Aminotransferase (serum glutamic oxaloacetic transaminase)
bpm	Beats Per Minute
BNP	Brain Natriuretic Peptide
BUN	Blood Urea Nitrogen
cAMP	Cyclic Adenosine Monophosphate
CI	Cardiac Index (L/min/m^2)
CO	Cardiac Output (L/min)
Control	Inhaled 0.9% sodium chloride solution, USP administered via the VentaProst delivery system
CFR	Code of Federal Regulations
C_{max}	Maximum Concentration
CPB	Cardiopulmonary Bypass
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-Reactive Protein
CSR	Clinical Study Report
CNTS	Continuous Nebulization Tube Set
CVP	Central Venous Pressure (mm Hg)
DCF	Data Collection Form

Abbreviation	Term
DNR	Do Not Resuscitate
dPAP	Diastolic Pulmonary Arterial Pressure (mm Hg)
dSAP	Diastolic Systemic Arterial Pressure (mm Hg)
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
ESR	Erythrocyte Sedimentation Rate
ETT	Endotracheal Tube
FDA	Food and Drug Administration
FiO_2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
HME	Heat-Moisture Exchanger
HR	Heart Rate (bpm)
IABP	Intra-aortic Balloon Pump
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IL-6	Interleukin 6
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
LAR	Legally Authorized Representative
LDR	Lung Dosing Rate
LFT	Liver Function Test
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute
mPAP	Mean Pulmonary Arterial Pressure (mm Hg)
mSAP	Mean Systemic Arterial Pressure (mm Hg)
NC	Nasal Cannula
ng	Nanogram
OR	Operating Room
OTC	Over-the-Counter
PAH	Pulmonary Arterial Hypertension
PaO_2	Partial Pressure of Oxygen in Arterial Blood
PAP	Pulmonary Arterial Pressure (mm Hg)
PCWP	Pulmonary Capillary Wedge Pressure
PD	Pharmacodynamic
PEEP	Positive End Expiratory Pressure
PH	Pulmonary Hypertension
PIP	Peak Inspiratory Pressure
PK	Pharmacokinetic
PP	Per Protocol

Abbreviation	Term
PGI_2	Prostaglandin I_2 (epoprostenol)
PVR	Pulmonary Vascular Resistance (dyn/sec/cm^5)
RBC	Red Blood Cell (count)
RH	Right Heart
RHF	Right Heart Failure
RT-PCR	Reverse Transcription Polymerase Chain Reaction
RVSWI	Right Ventricular Stroke Work Index
SAE	Serious Adverse Event
SaO_2	Arterial Oxygen Saturation
sPAP	Systolic Pulmonary Arterial Pressure (mm Hg)
sSAP	Systolic Systemic Arterial Pressure (mm Hg)
SE	Standard Error
SOP	Standard Operating Procedures
SOC	Standard of Care
SpO_2	Oxygen Saturation by Pulse Oximetry
Study Drug	Active or Control Treatment
SVR	Systemic Vascular Resistance
TEAE	Treatment-Emergent Adverse Event
TEE	Transesophageal Echocardiogram
TPG	Transpulmonary Gradient
$t_{1/2}$	Half-Life
TLD	Total Lung Dose
ULN	Upper Limit of Normal
VA-ECMO	Veno-arterial Extracorporeal Membrane Oxygenation
VentaProst	VentaProst™ – Drug/device combination product consisting of aerosolized epoprostenol delivered via dedicated drug delivery system
VentaProst Nebulizer	The nebulizer assembly that is part of the VentaProst delivery system
VTE	Venous Thromboemobolism
VV ECMO	Venovenous Extracorporeal Membrane Oxygenation
WBC	White Blood Cell (count)
WHO	World Health Organization

2.1 Introduction

COVID-19 is a rapidly emerging pathogen that has recently been declared a pandemic by the World Health Organization (WHO). No targeted therapeutic treatments for coronavirus (COVID-19) have been identified. Symptoms range from mild upper respiratory tract infection to profound hypoxia, severe pneumonia, ARDS and death. Progression of end stage disease is unpredictable with high fatality rates in mechanically ventilated patients as a result of multi-organ failure. Among patients who require hospitalization, mortality may be 5% to 15%, and for those who become critically ill, reported mortality ranges from 22% to 62%.

Prostacyclin therapy—available in oral, inhaled, and intravenous forms—is an analogue which mimics endogenous prostacyclin (PGI2). Prostacyclin binds to its receptor (a G-protein coupled receptor) found on the surface of vascular smooth muscle and platelets, activates cyclic adenosine monophosphate (cAMP), and results in inhibition of platelet aggregation, vascular smooth muscle relaxation and vasodilation of the pulmonary arteries (Mitchell, Ali et al. 2008). Prostacyclins are most commonly used in the treatment of PAH due to their potent vasodilatory effects. In addition, prostacyclin analogs also inhibit platelet aggregation and may reduce prothrombotic effects of endothelin.

The rationale for use of vasodilators in COVID-19 patients rests on their rapid local effect on the pulmonary vasculature, which has shown to lead to increased oxygenation in other diseases, such as PAH (Higenbottam, Wheeldon et al. 1984) and post-surgical PH (De Wet, Affleck et al. 2004). Epoprostenol has the additional advantage over inhaled nitric oxide in that it may be directly administered through a standard ventilator (closed-circuit).

The rationale for aerosolized prostacyclin use in COVID-19 patients experiencing hypoxia leading to cardiac failure is two-fold:

(1) inhaled prostacyclin therapy has been used in the treatment of ARDS and has been shown to improve oxygenation and ventilation-perfusion mismatch (see Section 9). Prostacyclins, such as epoprostenol, promote pulmonary vasodilation via a cyclic adenosine monophosphate-mediated decrease in intracellular calcium (Figure 4). While it has not been associated with improved outcomes, such as mortality, and it's use in ARDS is off-label, it may be used in severe life-threatening hypoxemia refractory to conventional ARDS management, such as has been seen in COVID-19.

(2) The second potential benefit of prostacyclin therapy in the management of COVID-19 is to mitigate direct SARS-CoV-2-associated coagulopathy. Prostacyclins have anti-inflammatory (Dewachter 2012) and antiplatelet aggregation properties[1]. Microvascular thrombosis and large vessel venous thromboembolism have been described anecdotally and in case reports of corona virus infected patients and abnormal coagulation parameters are associated with increased mortality (Giannis, Ziogas et al. 2020). Inhibition of platelet aggregation occurs with prostacyclin therapy and may mitigate thrombosis in situ seen in PAH itself, and potentially in patients with COVID-19 associated respiratory illness.

Literature data with both inhaled NO and inhaled epoprostenol in ARDS, acute lung injury and severe hypoxemia show improvement of oxygenation (Afshari, Bastholm Bille et al. 2017), (Dzierba, Abel et al. 2014), decrease of pulmonary arterial pressure (Fuller, Mohr et al. 2015) and in some cases improvement in clinical outcomes such as shorter time on mechanical ventilation and shorter time in ICU (Ammar, Bauer et al. 2015). However, due to the heterogeneity of the population and the severity of the disease, not all studies agree on the effectiveness of inhaled epoprostenol, particularly to reduce mortality in ARDS (Adhikari, Dellinger et al. 2014), (Afshari, Bastholm Bille et al. 2017). Meta-analyses have concluded that the quality of the currently published data for the use of inhaled vasodilators in ARDS, ALI and refractory hypoxemia is insufficient to definitely conclude for or against their use (Afshari, Bastholm Bille et al. 2017), (Fuller, Mohr et al. 2015).

This study will evaluate the potential therapeutic benefit of VentaProst in treating patients with COVID-19 at risk for the progression of respiratory and/or cardiac/circulatory failure. This double-blind, placebo controlled study will assess the efficacy and safety of VentaProst at a range of 3.4-30.6 ng/kg/min for a maximum of 10 days at the discretion of the Investigator. The patient will be followed through Day 28 to assess their clinical status.

2.2 VentaProst

2.2.1 Nonclinical Experience

Refer to the current Investigator's Brochure (IB) for details of nonclinical pharmacology and toxicology studies with VentaProst.

2.2.2 Clinical Experience

There have been no clinical trials to date with VentaProst in COVID-19 patients (see Section 2.2.4 below for summary of clinical data with VentaProst in cardiac surgery patients).

2.2.3 Summary of Pharmacokinetic Results

Epoprostenol undergoes rapid chemical hydrolysis under physiological conditions to yield 6-keto-PGF1α and is also subject to enzymatic degradation. As such, it is only possible to evaluate the PK using radioactively labeled drug. Studies using 3H-epoprostenol sodium indicate half-life is generally less than 3 minutes with an I.V. bolus, and with I.V. infusion, plasma steady-state concentrations were achieved within 15 minutes of initiation of the infusions, and steady-state concentrations increased linearly with increasing infusion rate. Tissue distribution studies indicate the highest levels of radioactivity were observed in the kidney, liver, and small intestine and the lowest levels were observed in brain and adipose tissue. Epoprostenol-derived material is rapidly excreted into urine and feces after dosing with epoprostenol sodium.

There is only one study in the literature that reports the PK of inhaled epoprostenol. The study by Haraldsson (Haraldsson, Kieler-Jensen et al. 2000) was designed to evaluate the effects of inhaled epoprostenol on platelet aggregation after surgery. No differences were seen in 6-keto-PGF1α levels with two dose levels of epoprostenol compared to placebo

over six hours of administration in the ICU. Epoprostenol deposition in the lungs was not quantified, but the aerosol was administered only during the inspiratory phase of mechanical ventilation. The blood levels of 6-keto-PGF1α by enzyme immunoassay in this study were reported to be several times higher than other levels reported in the literature.

In 2017, Stanford University's Department of Cardiac Surgery conducted an observational study (IND129777, Report# APC-VP-CLN-004) investigating the levels of 6-keto-PGF1α in cardiac surgery patient requiring CPB. Sixteen patients were enrolled; eight did not received inhaled epoprostenol, eight received aerosolized epoprostenol at a nominal starting dose of 50 ng/kg/min.

Plasma levels determined in aerosol epoprostenol naïve patients indicates that cardiac surgery procedures, including CPB, result in elevated endogenous levels of both 6-keto-PGF1α and thromboxane B2. Delivery of aerosol epoprostenol in patients resulted in a further elevation of 6-keto-PGF1α levels, but not thromboxane B2.

While it proved difficult to delineate the endogenous and exogenous contributions of aerosol delivery during surgery, 6-keto-PGF1α levels declined rapidly in aerosol naïve patients during ICU stay. Examination of the 6-keto-PGF1α levels during weaning, after this endogenous decline, indicate that the overall aerosol delivery efficiency, nebulized to absorbed (deposited lung dose), is less than 8%. That is, out of a nominal dosing rate of 50 ng/kg/min only 4 ng/kg/min actually reaches the lungs and gets absorbed.
Comparison to recently published data (Nicolas, Krause et al. 2012) investigating 6-keto-PGF1α levels during steady state I.V. administration of Flolan indicates that the systemic exposure from aerosol delivery in cardiac surgery is similar to, or lower, than that experienced from intravenous administration of the approved Flolan product.

The findings of this observational PK study with inhaled epoprostenol are sufficient to make a correlation to historical systemic exposure levels with intravenous administered Flolan (the reference listed drug) and show levels of exposure similar to, or lower than, the currently approved intravenous product.

2.2.4 Summary of Clinical Results

The safety and tolerability of VentaProst were evaluated in a Phase 2a Clinical Study in cardiac surgery patients "*A Two-Part Pharmacodynamic Study to Compare VentaProst™ (Epoprostenol Solution for Inhalation via Custom Drug Delivery System) Dosing to Conventionally Administered Aerosolized Epoprostenol Dosing in Cardiac Surgery Patients*" (NCT03122730).

Overall, 15 patients were exposed to doses of VP from 3.4 to 20.4 ng/kg/min in this study. Administration of VP in this dose range was well-tolerated. Overall, there were 2 patients (28.6%) in Part I and 1 patient (12.5%) in Part II who experienced a total of 7 TEAEs. All 7 TEAEs were assessed by the investigator as related to the surgical procedure and as unrelated to the study drug and unrelated to the device. No deaths occurred during the study. A total of 3 patients had 1 SAE each. All 3 SAEs were considered to be unrelated to the study drug or the study device.

Seven patients were evaluated in Part I to determine the effective dose equivalence between VP delivered at 17 ng/kg/min and off-label aerosolized Veletri administered at 50 ng/kg/min during mechanical ventilation. In all patients, VP 17 ng/kg/min was found to be equivalent either by calculation of effect compared with aerosolized Veletri 50 ng/kg/min or the investigators' judgement. In most patients, no differences were observed in oxygen saturation ranges between VP and aerosolized Veletri treatments at the same FiO2 while on the ventilator. The investigator determined that oxygenation, assessed by oxygen saturation measurements, did not change disproportionately with ventilator operating parameters on VP compared with aerosolized Veletri.

Eight patients were evaluated in Part II of the study to identify the optimal dose of VP. In the investigator's judgement, the optimal VP dose was determined to be 6.8 ng/kg/min in 2 patients, 10.2 ng/kg/min in 3 patients, and 13.6 ng/kg/min in 3 patients, which is the minimal dose that reliably produced a maximum hemodynamic response in all patients.

There have been no clinical trials to date with VentaProst in COVID-19 patients.

See IB for additional clinical information regarding inhaled epoprostenol.

2.2.5 Summary of Known and Potential Risks of Inhaled Epoprostenol Administration

Safety of inhaled epoprostenol in cardiothoracic surgery patients is remarkable. In the reported literature to date, there were no reports of serious or life-threatening drug-related safety events. Due to its mechanism of action, inhaled epoprostenol may theoretically cause increased bleeding (anti-platelet mechanism) or systemic vasodilation consequent to spill over into the central circulatory system, but no such events have been reported. Some accounts of the use of inhaled prostacyclin in the chronic setting (e.g. iloprost for PAH) report transient events as listed on the approved product labeling. These include cough, headache, flushing, and an influenza-like syndrome. However, these types of events are unlikely to be reported due to sedation in the ICU setting.

VentaProst may result in hypotension, which will be monitored via frequent - assessments of oxygenation, ventilatory and hemodynamic parameters and vital signs. Pulmonary edema and pulmonary bleeding are potential risks due to the drug's mode of action (refer to Section 7.2.2). Worsening oxygenation is a theoretic concern through worsened ventilation/ perfusion matching. This will be monitored through continuous pulse oximetry throughout the administration of the inhaled epoprostenol.

Risks to subjects in this study are related to common procedures performed (e.g., venipuncture) and the documented adverse events (AEs) listed in the current Investigator's Brochure. These risks are communicated to the subjects in the consent forms. There may be additional risks that are currently unknown.

The benefits of the study may include targeted lung vasodilation and improved oxygenation, potential anti-platelet effects on the lung vasculature, reduction in disease progression, avoidance of greater oxygen needs and early weaning off mechanical ventilation. If the drug does have such properties, then this may aid recovery, improve

outcomes and enable an earlier discharge from the hospital.
There is no funding awarded to the patients participating in this study.

2.2.6 Dosing Rationale for VentaProst

Literature on the current use of aerosolized epoprostenol in cardiac surgery and in ARDS shows a wide range and technically variable dosing for lowering PVR (Rao, Ghadimi et al. 2018), (Kallet, Burns et al. 2017), (Fuller, Mohr et al. 2015). Most of the experience is with continuous nebulization by commercially available nebulizers in various positions in mechanical ventilator circuits at doses of 50 ng/kg/min. Unlike the commercially available nebulizer systems, the VentaProst delivery platform aerosolizes epoprostenol only during the inspiratory cycle of the ventilator and administers respirable sized aerosol droplets (3-5 μm) in close proximity to the ETT of mechanically ventilated patients.

The assumed effect of the current continuous dosing regimen of 50 ng/kg/min is that the hemodynamic response is maximized and that no further improvements would be seen by increasing the dose. The initial in vitro estimate of the equivalent VentaProst (VP) dose to a 50 ng/kg/min conventional dose of continuously aerosolized Veletri was 17 ng/kg/min, which was the starting dose in Part I of the APC-VP-CLN-001 Phase 2a study conducted by Aerogen Pharma. During Part I of the study, it was determined that this dose is equivalent to 50 ng/kg/min epoprostenol delivered off-label via a generic nebulizer and continuous delivery. In Part II of the APC-VP-CLN-001 Phase 2a study, the VP dose escalation started from an initial dose of 3.4 ng/kg/min (20% of the equivalent dose). The dose was then increased in 3.4 ng/kg/min increments. Part II of the study was designed to demonstrate that the dose-response plateau could be achieved using lower VP doses than the initial estimated equivalent dose in Part I. Doses up to 30.6 ng/kg/min were approved for use in the study. In Part I of the study one patient, per the investigator discretion, received a 20.4 ng/kg/min dose. In Part II of the study it was determined that the optimal VP dose of 6.8 ng/kg/min in 2 patients, 10.2 ng/kg/min in 3 patients, and 13.6 ng/kg/min in 3 patients provided stable hemodynamic response. Based on these data, the recommended starting dose of VP, will be 13.6 ng/kg/min, as this dose is anticipated to produce the maximum hemodynamic response.

The proposed nominal dosing regimen for this COVID-19 trial is for up to 10 days of breath-synchronized aerosol delivery with a starting dose of study drug 13.6 ng/kg/min. Based on hemodynamic and oxygenation parameters, the dose can be titrated in 3.4 ng/kg/min steps up to a maximum of 30.6 ng/kg/min or down to a minimum of 3.4 ng/kg/min while patients are on mechanical ventilation. Of this nominal dosing rate approximately 30% will reach and deposit in the lung. Thus, the maximum Lung Dosing Rate (LDR) is ~10 ng/kg/min and the maximum Total Lung Dose (TLD) is ~ 144 μg/kg (Refer to VP IB Edition 6 dated 17-Jun-2020).

The inhalation toxicology program for VentaProst, originally designed for the cardiac surgery indication, covered a maximum LDR of 320 ng/kg/min and 60 ng/kg/min and a maximum TLD of 1091.4 μg/kg and 172.8 μg/kg in rats and dogs respectively. The LDR and TLD margins over the proposed maximum clinical exposure are thus 32 and 6, and 7.6 and 1.2, in rats and dogs respectively.

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is the reduction of respiratory, cardiac or circulatory failure in patients with confirmed COVID-19.

3.2 Secondary Objectives

The secondary objective in this study is to evaluate the effects of VentaProst on improvement in oxygenation, improvement in clinical outcomes and safety and tolerability.

The study will also evaluate the effects of VentaProst on inflammatory parameters in subjects with confirmed COVID-19.

3.3 Study Design

This is a double-blind, placebo controlled study of VentaProst (Active) as compared to placebo (Control). Active is inhaled epoprostenol administered via the VentaProst delivery system in 10 COVID-19 positive patients. Control is inhaled 0.9% sodium chloride solution administered via the VentaProst delivery system in 10 COVID-19 positive patients. Throughout the remainder of the protocol both Active and Control will be referred to as "study drug". This study will evaluate the potential therapeutic benefit of VentaProst in treating patients with COVID-19 who require mechanical ventilation and are at risk for the progression of respiratory and/ or cardiac/circulatory failure. This study will assess the efficacy and safety of VentaProst at an initial dose of 13.6 ng/kg/min (A range from 3.4-30.6 ng/kg/min may be administered as clinically required for a maximum of 10 days at the discretion of the Investigator. Patients will be followed through Day 28 to assess clinical outcomes.

Patients will be consented and randomized to either the Active or Control group within 24 hours of being placed on mechanical ventilation. Patients will be administered study drug using the VentaProst delivery system which allows up and down titration of study drug to achieve hemodynamic and oxygenation stability. The starting dose of study drug will be initiated at 13.6 ng/kg/min. Based on hemodynamic and oxygenation parameters, the dose of study drug can be increased in 3.4 ng/kg/min increments up to a maximum of 30.6 ng/kg/min or down to a minimum of 3.4 ng/kg/min.

All study staff with the exception of the unblinded pharmacist and Sponsor CRA will be blinded to which treatment regimen a patient has been assigned. Titration and weaning will be performed the same for all patients. Study drug will be administered based on the pump rate calculated for active treatment in mL/hr. Titration guidelines are provided in Section 5.3.3 and Table 3.

3.4 Duration of Participation

Patients who meet entry criteria will be entered into the study and the duration of study participation for each patient is listed below. The duration of study participation for each patient is as follows:

- Screening: up to 14 days
- Treatment: up to 10 days
- Follow up: 28 days

4. SELECTION AND WITHDRAWAL OF PATIENTS

Approximately 20 COVID-19 positive patients requiring mechanical ventilation will be enrolled in this study. Ten study participants will be randomized to either Active (inhaled epoprostenol administered via the VentaProst delivery system) treatment or Control (inhaled 0.9% sodium chloride solution administered by the VentaProst delivery system at calculated rates (mL/hr) used for the aerosolized epoprostenol). Study drug will indicate both Active and Control treatments.

Patients who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to enroll into the study.

4.1 Inclusion Criteria

Patients are eligible for this study if they meet all of the following criteria:

1. Women and Men Age ≥18 years old (no upper limit)
2. Confirmed COVID-19 positive by RT-PCR test
3. Patients who require invasive mechanical ventilation.
4. Enrolled into study within 24 hours of being placed on mechanical ventilation
5. Consent or professional consent obtained
6. Duration of shortness of breath must be within the previous 14 days.
7. Female subjects of childbearing potential must have a negative pre-treatment pregnancy test (serum or urine).
8. Received or currently receiving dexamethasone therapy for COVID-19
9. Willing and able to comply with treatment schedule and follow-up.

4.2 Exclusion Criteria

Patients are **NOT** eligible for this study if they meet any of the following criteria:

1. Patients on ECMO support.
2. Patients receiving another inhalation research medication or inhaled nitric oxide.
3. Not expected to survive for 48 hours.
4. Pregnant (positive pregnancy test in a pre-dose examination) or breastfeeding
5. Open tracheostomy.
6. Clinical contra-indication, as deemed by the attending physician.
7. Allergy to Epoprostenol and its diluent
8. Using inhaled vasodilators at baseline.
9. Patients who are hemodynamically unstable as determined by investigator
10. Patients with significant hemoptysis as determined by investigator

4.3 Re-Screening of Patients

Patients may not be enrolled more than once.

4.4 Removal of Patients from Therapy or Assessment

Aerogen Pharma or the Investigator may discontinue patients from the study at any time for safety or administrative reasons.

The End of Treatment Study procedures (Day 10) are to be completed for all patients who discontinue from the study (except Screen Failure patients).

The Investigator will promptly explain to the patient or their LAR that the study will be discontinued for the patient and provide appropriate medical treatment and other necessary measures for the patient.

Patients who discontinue early from the study will be discontinued for one of these primary reasons: Adverse events, patient death, lost to follow-up, patient withdrew consent, protocol violation, lack of efficacy, investigator decision, study terminated by sponsor, screen failure, or other. Study disposition information will be collected on the Patient Disposition DCF.

4.4.1 Criteria for Stopping VentaProst Treatment

Individual patients stopping criteria: At any time during study drug administration , patients may be removed from study treatment and placed on standard of care (SoC) therapy if they meet one or more of the following pre-defined criteria leading to a deterioration in their condition:

- Severe hypotension as evidenced by a systolic BP < 90 mmHg or MAP < 60 mmHG for >2 hours from the start of VentaProst
- Need for VV ECMO
- Need to increase existing vasopressor therapy by more than 25%
- Worsening oxygenation, ventilatory, or hemodynamic parameters that in the opinion of the investigator the patient should be removed from study treatment
- Massive hemoptysis thought to be clinically significant and not due to endotracheal tube trauma
- Pulmonary Edema
- If a clinically inadequate response is observed

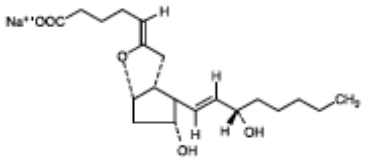
Study stopping criteria: If 3 patients are removed from the study for any of the above conditions, the study will stop further enrollment and investigation will be conducted to determine the cause of the events. An independent safety evaluation will also be conducted. If it is suspected that the investigational product has caused the events, the study will be terminated.

Independent Safety Evaluation: Independent safety evaluation will be conducted by a licensed physician who is not involved in the VentaProst COVID-19 clinical study or the sponsoring organization.

5. STUDY TREATMENTS

5.1 Identity of Medication Component of the Investigational Product

The study medication VentaProst, Flolan (epoprostenol sodium), is manufactured by GlaxoSmithKline and has been analyzed and released according to their specifications. The labelling of Flolan and placebo for this clinical trial will follow the protocols and procedures set forth by OSU's Investigational Drug Services (IDS). The Control for this study is 0.9% sodium chloride solution, USP from the OSU IDS stock and will be labeled in a blinded manner per the IDS protocols for maintenance of study blind.

Drug Substance Name	Epoprostenol Sodium
Chemical Name	5Z,9α,11α,13*E*,15*S*)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-1-oic acid.
Molecular Formula	$C_{20}H_{31}NaO_5$
Structural Formula	
Molecular Weight	374.45

5.1.1 Storage Condition

Both the vials of study medication and sterile diluent buffer should be stored between 20º to 25ºC (68º to 77ºF) with excursions permitted to 15° to 30°C (59° to 86°F) and kept in the supplied carton to protect the product from light. Study medication will be stored in a secure, controlled-access location at the study sites.

The 0.9% sodium chloride solution will be stored according the the product labelling.

5.2 Treatments Administered

Patients will receive study drug via mechanical ventilator, starting at 13.6 ng/kg/min. If determined by the treating physician, study drug can be up titrated in 3.4 ng/kg/min increments to a maximum of 30.6 ng/kg/min or down to a minimum of 3.4 ng/kg/min. At the Investigator's discretion, the patient will be weaned off the drug in 3.4 ng/kg/min increments. Study drug will be administered based on the pump rate calculated for the active treatment but delivered in mL/hr. Study drug can be administered up to 10 days.

5.3 Study Medication Supply, Preparation, and Administration

5.3.1 Study Medication Supply

The medicinal component of VentaProst, Flolan, (epoprostenol sodium), is already approved for I.V. delivery. The dosage form is a vial of 1.5 mg epoprostenol as a

lyophilizate and the required pH 12 Sterile Flolan diluent per the currently approved packet insert (NDA20-444/ Supplement 24[1]). Flolan and its diluent (pH 12 Sterile Diluent) are not re-formulated by Aerogen Pharma. Flolan is used with the same diluent system and reconstituted per the approved packet insert.

Flolan and diluent container closure (glass vial and stopper/crimp-pH 12 Sterile Diluent for Flolan comes in a plastic bottle for mixing) and secondary packaging (cardboard box) are not being altered, including the information on the vial and box label and the information in the approved Flolan packet insert. This preserves the approved drug labeling information per NDA 20-444.

Placebo will be a corresponding volume of 0.9% sodium chloride solution from the OSU IDS stock.

5.3.2 Study Medication Preparation

Refer to the VentaProst-COVID Pharmacy Manual for preparation of study drug solution..

Prior to use, drug solutions must be protected from light and refrigerated at 2° to 8°C (36° to 46°F) if not used immediately. Do not freeze drug solutions and discard any drug solution that has been frozen. Discard any drug solutions if refrigerated for more than 8 days. Control, (0.9% sodium chloride solution) will be placed in identical syringes and masked according OSU IDS procedures for blinded studies.

5.3.3 Study Medication Administration

In the ICU, patients will be started on study drug administered via the VentaProst delivery system at an initial dose administered at 13.6 ng/kg/min. Study Drug Study drug may be titrated up or down in 3.4 ng/kg/min increments (refer to VentaProst Pharmacy Manual) as clinically indicated to a dose range of 3.4-30.6 ng/kg/min. Study drug will be administered based on the pump rate calculated for the active treatment in mL/hr. Study drug can be administered up to 10 days.

[1] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020444s024lbl.pdf

Table 3: Administration Titration Guidelines

Up titration Guideline	Downward Titration / Guideline
Start Dose: 13.6 ng/kg/min 1st Step Up Dose (17.0) 2nd Step Up Dose (20.4) 3rd Step Up Dose (23.8) 4th Step Up Dose (27.2) 5th Step Up Dose (30.6)	Start Dose: 13.6 ng/kg/min 1st Step Down dose (10.2) 2nd Step Down Dose (6.8) 3rd Step Down dose (3.4)

All study drug will be administered per the calculated pump rate for the active treatment in ml/hr

Table 4-Example of Up Titration for male with Ideal Body Weight of 70 kg

Initial Dose Rate	Initial Pump Rate	New Dose Rate	New Pump Rate
13.6 ng/kg/min	1.89 mL/hr	13.6 ng/kg/min	1.89 mL/hr
		17.0 ng/kg/min	2.39 mL/hr
		20.4 ng/kg/min	2.86 mL/hr
		23.8 ng/kg/min	3.33 mL/hr
		27.2 ng/kg/min	3.81 mL/hr
		30.6 ng/kg/min	4.28 mL/hr

Active drug is prepared with 50 mL in each syringe at a concentration of 30,000 ng/mL.
All study drug will be administered per the calculated pump rate for the active treatment in ml/hr.

5.3.4 Study Medication Weaning

Patients will be weaned from study drug slowly to avoid rebound vasoconstriction. During weaning, doses will be decreased in steps of 3.4 ng/kg/min increments, with a minimum of 15 minutes between changes. The weaning process should occur in isolation to other treatment changes (no changes in inotropes, vasopressors, or vasodilators) whenever possible. Patients will be observed closely before, during, and after dose changes. In the event patients demonstrate signs of hemodynamic instability or a decrease in oxygenation indicated by pulse oximetry during downward titration, the dose will be returned to its previous level. Once patients have been stable for at least 15 minutes, repeat attempts at dose reduction may be undertaken. The process will continue until patients are fully weaned. Patients will be monitored for safety and efficacy throughout study drug administration.

5.4 Identity of the Device Component of the Investigational Product

5.4.1 Identity of Device

The Phase 2a VentaProst drug delivery system is designed to accurately and precisely administer aerosol to the lungs of critically ill patients who require support via mechanical ventilation. The aerosol generator's fundamental operating mechanism and materials of construction will be similar to the 510(k)-cleared Aeroneb Solo System (K120939, K103635, K070642, Aerogen Ltd) and it is being designed for compatibility with the range of ventilators found in the OR and ICU.

5.4.1.1 VentaProst Aerosol Delivery to Ventilated Patients

The VentaProst delivery system (Figure 1) consists of reusable and single-patient use disposable elements:

1. Reusable multi-patient use components consist of two electronic controllers with power supplies, Aerogen Solo Nebulizer Cable, and Sensirion Flow Sensor Cable. When used together, they synchronize aerosol generation with the patient's inspiratory pattern through a single-patient use, disposable administration kit.
    - Aerogen Pro-X, is a commercially available device (K120939[2]) cleared for use to continuously operate the disposable Aerogen Solo nebulizer. (item #1 Figure 1).
    - Aerogen Pharma Controller (AP Controller) is an investigational device, which synchronizes aerosol generation with the ventilator inspiratory cycle (item #2 on Figure 1). This controller was tested to demonstrate its safety for use under IND129777.
    - Aerogen Solo Nebulizer Cable
    - Sensirion Flow Sensor Cable
2. Single-patient disposable kit:
    - Aerogen Solo nebulizer (item #3 on Figure 1) is a commercially available, low mass and low profile vibrating mesh aerosol generator (K070642) cleared for use with the Aerogen Pro-X controller and Aerogen Continuous Nebulization Tube Set (CNTS).
    - Aerogen CNTS and syringe (items #4 and 5 on Figure 1) is a commercially available device (K103635) cleared for use to connect to the Aerogen Solo and deliver medication from the drug reservoir (syringe) to the mesh the nebulizer.
    - Flow sensor and cable connected to the Aerogen Pharma Controller (AP Controller, item #7 on Figure 1). This is a new component of the system, which was tested to demonstrate safety for use in a clinical study.

The VentaProst delivery system will be used in conjunction with a commercially available and FDA-cleared syringe pump (item #8 on Figure 1). In general, any available syringe pump, which (1) is compatible with the Aerogen Continuous Nebulization Tube Set (CNTS syringe and tubing), and (2) is capable of delivering medication to the vibrating mesh nebulizer within the range of 0.4 to 12.0 mL/h as required to deliver the doses specified in the APC-VPCOV-CLN-001 Pharmacy Manual. For purposes of the VPCOV study, Aerogen Pharma will supply the Perfusor® Space Infusion Syringe Pump System from B.Braun (Figure 1). This particular syringe pump is FDA-cleared (K093913), it is compatible with the CNTS syringe (items #4 on Figure 1) and is able to

[2] The product names for the Aerogen commercial products changed from the term "***Aeroneb***", to the brand name "***Aerogen***". A Note to File was submitted to FDA and receipt was acknowledged by the Branch Office

deliver fluids in the rage of 0.4 to 12.0 mL/h. It is worth noting that on 11 April 2020, this pump received EUA for use in the tracheal delivery of continuous nebulized medications into a nebulizer to treat patients of all ages with or suspected of having the Coronavirus Disease 2019 (COVID-19)[3].

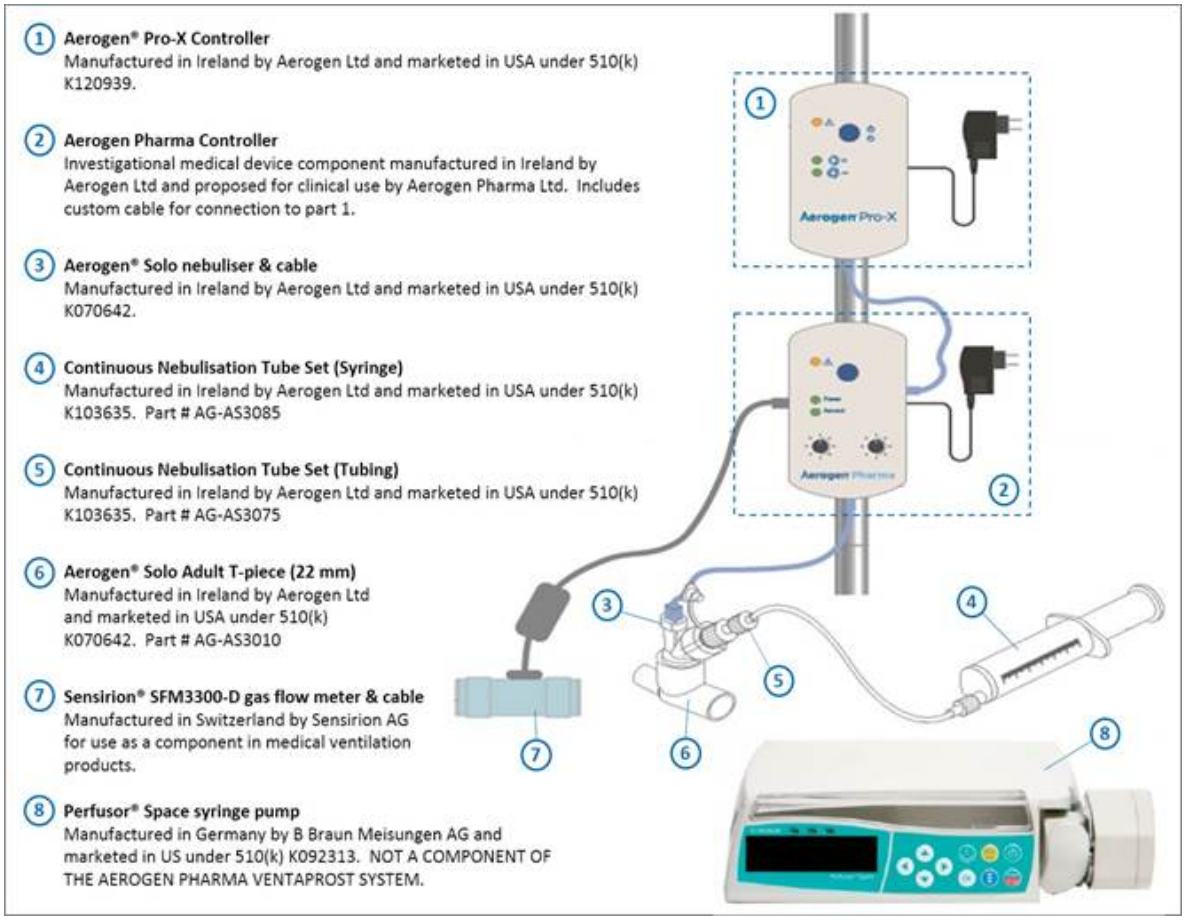


Figure 1: Drug Delivery System

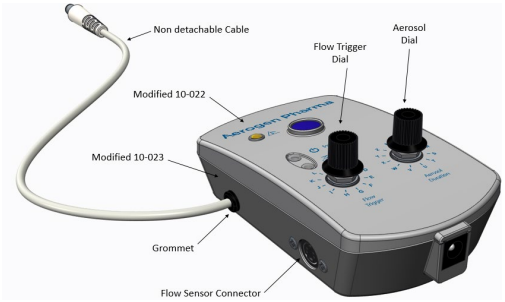
The Aerogen Pro-X (item #1, Figure 1), Aerogen Solo (item #3, Figure 1) are mounted on an I.V. pole at the patient's bedside. The two controllers and Aerogen CNTS (items #4 and 5, Figure 1) are routinely used as a system within their intended use. The sensor and nebulizer are connected into specific locations of the inspiratory limb of the ventilator pre- and post the humidifier, respectively (see Figure 2). The addition of the AP Controller and an off-the shelf Sensirion flow sensor enables the VentaProst system to synchronize aerosol delivery with the inspiratory cycle of the ventilator (Figures 1 and 2).

Figure 2 illustrates the AP Controller, which is similar to the commercially available

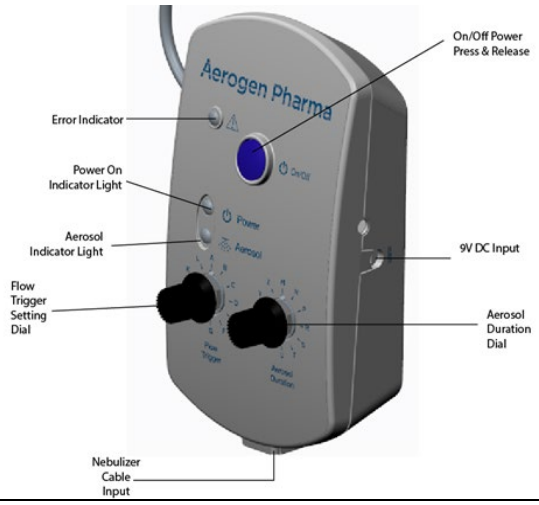
[3] https://www.fda.gov/media/136894/download

Aerogen Pro-X controller in form, size, weight and materials used for the upper and lower shells. The AP Controller uses the same AC/DC adapter and cable as used in the commercial Aerogen Pro-X controller. The packaging used for the AP Controller is same as packaging validated by Aerogen Ltd. for the commercially available Aerogen Pro-X system. Functionality of the AP Controller was tested in design verification studies (IND129777). Two dials (Figure 2) are used to: (1) set the flow threshold for nebulization triggering during the inspiratory cycle of the ventilator, accommodating initial ventilator baseline bias flows, and (2) set the duration of nebulization during the inspiratory cycle (a detailed description of the mechanism of action of the AP Controller is presented in IND129777).

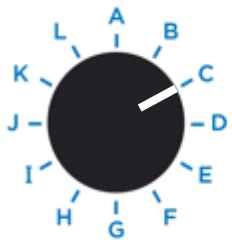
A. Diagram of Aerogen Pharma Controller (left side view)



B. Diagram of Aerogen Pharma Controller (right side view)



C. Flow Trigger Dial settings



A	2.5slm
B	4.0slm
C	5.5slm
D	7.0slm
E	8.5slm
F	10.0slm
G	11.5slm
H	13.0slm
I	14.5slm
J	16.0slm
K	17.5slm
L	19.0slm

D. Aerosol Duration Dial settings

M	0.3sec
N	0.4sec
P	0.5sec
R	0.6sec
S	0.7sec
T	0.8sec
U	0.9sec
V	1.0sec
W	1.1sec
X	1.2sec
Y	1.3sec
Z	1.4sec

Figure 2: Aerogen Pharma Controllers

Prior to administration, study drug will be prepared per the VP COVID Pharmacy Manual and placed into a 60 mL CNTS syringe. The syringe will be labeled to maintain the study blind. The user will attach the syringe to the CNTS tubing and prime the tube set so that the formulation reaches the Aerogen Solo, producing aerosol generation. The CNTS syringe set will be placed in a B Braun Perfusor Space Infusion syringe pump. The 15-mm T-Piece with nebulizer is placed between the ventilator circuit and the ETT (Figure 2). The user will select the pump rate (mL/hr) to deliver the recommended dose based on

the ideal body weight in kilograms (kg) dispensed to achieve the dose rate in ng/kg/min for active treatment. The control treatment's corresponding pump flow rate in mL/hour will be calculated based on initial dose of Flolan in ng/kg/min. All study drug will be administered per the calculated pump rate for active treatment in ml/hr. The user will be able to adjust this recommended dose up or down (per protocol) by changing pump rate prior to selecting dose and initiating delivery. The selected dose will then be dispensed by the pump to the receiving surface of the mesh, resulting in generation of an aerosol with a volume median diameter in the range of 2 to 5 µm. The Aerogen Pharma Controller monitors the patient's breathing pattern and user adjusts the knob (on left) to initiate aerosol generation at the beginning of the breathing cycle. The knob on right sets the duration of aerosol generation within each breath.

The VentaProst device is designed to be compatible with standard intensive care unit (ICU) equipment. The following site-specific equipment will be needed to deliver the therapy: B.Braun syringe pump (provided by Aerogen Pharma), ventilator, endotracheal tube (ETT), humidifier, ventilator circuit. This equipment is standard for critical care medicine.

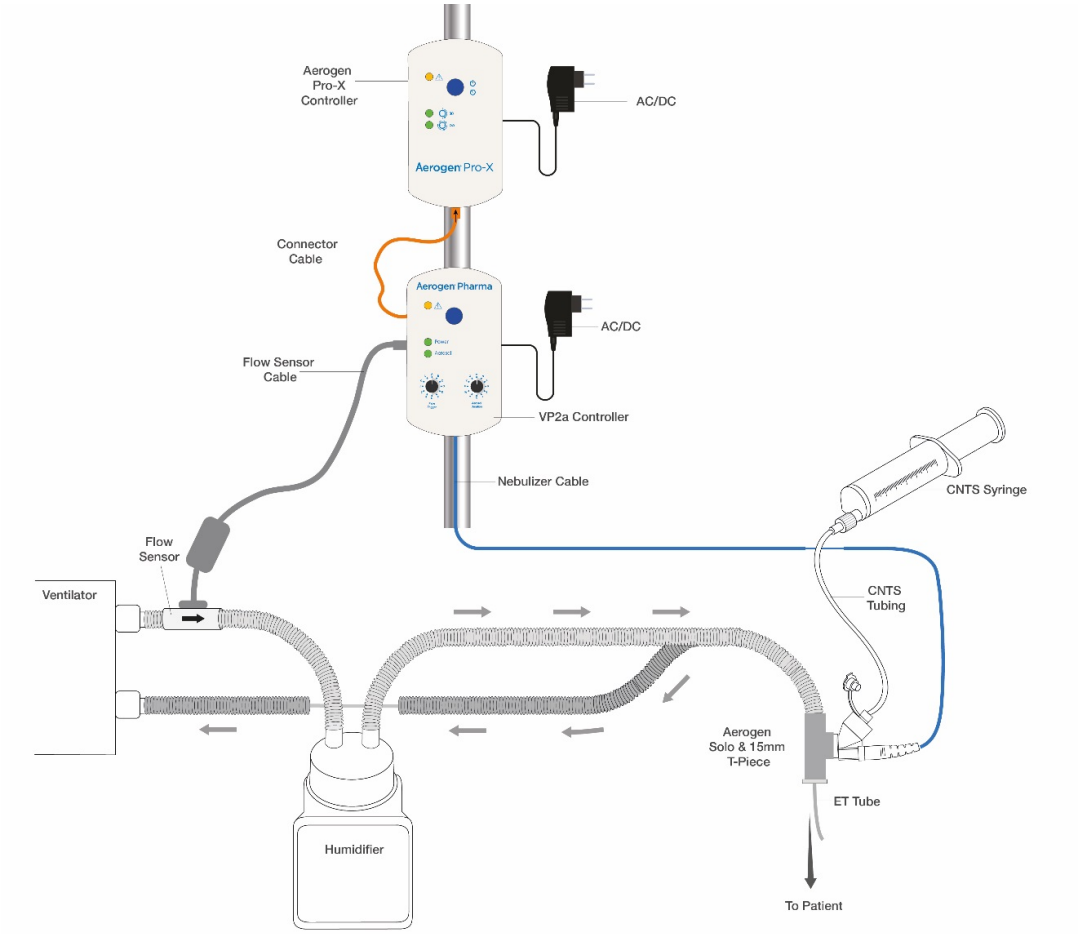


Figure 3 - VentaProst Device Placement in the Gas Pathway

5.4.2 Ventilator Settings

The device is designed for use with standard adult ventilator settings. An intermittent positive pressure ventilatory mode (i.e., not constant positive airway pressure [CPAP] or t-piece) is required to activate the device to deliver aerosol during the inspiration phase. A Heat-Moisture Exchanger (HME) may be used in the device circuit.

The site will utilize OSU's Standard of Care (SOC) mechanical ventilation guidelines for care of patients for COVID-19 with ARDS. The following ventilator parameters will be assessed daily while on VentaProst: Ventilator type, Mode, FiO_2, Inspiratory Time, Mean Airway Pressure, Peak Inspiratory Pressure, Positive End Expiratory Pressure, Respiratory Rate and Tidal Volume.

5.4.3 Device Supply

All device supplies will be provided by Aerogen Pharma Limited (including the B.Braun Syringe Pump). The serial numbers for the controllers, flow sensor, and nebulizer will also be recorded in an IP accountability dispensing log.

Used and unused devices will be inventoried and returned to the Sponsor or Sponsor's designee.

5.4.4 Device Replacement

Devices may be replaced at any time if there a suspicion of malfunction, but must be replaced if:

- The investigator suspects that, due to device malfunction, less than 90% of the total dose of study drug has been delivered. Reduced doses must be estimated and recorded in the patient's medical record and source documentation.
- The investigator suspects the device is not performing optimally for any reason.

5.4.5 Device Malfunction or Failure

One device (Aerogen Pro-X controller, Aerogen Pharma Breath Controller, Flow Sensor, Solo nebulizer, CNTS tubing and syringe, and associated components) is expected to perform throughout the duration of study treatment. If the controllers, Flow Sensor, CNTS tubing and syringe, or the Solo nebulizer are not functioning optimally for any reason, instructions for trouble-shooting provided in the device instruction for use manual should be followed. If one or more devices need to be replaced, the reason should be documented in the patient's medical record, dispensing log, and Device Performance Issues Form. Additional devices are provided for this purpose. The unique serial numbers of the new components will be recorded in the patient's medical record, dispensing log, and the source documentation.

For device malfunction or complaints, complete the Device Performance Issues Log and submit to the Sponsor at Complaints@aerogenpharma.com within 48 hours. Failed devices will be set aside from the general supplies, inventoried and returned to the Sponsor or the Sponsor's designee.

5.5 Blinding

Clinical and research staff and Sponsor will be blinded to Active or Control dose assignments with the exception of the pharmacy staff and an unblinded Sponsor CRA. Should unblinding be necessary, the medical monitor for this study will work with the unblinded pharmacist or unblinded CRA to unblind the patient.

Active treatment (Flolan) is clear in color when reconstituted and Control treatment (0.9% sodium chloride solution) is also clear in color to maintain the study blind. The Control and Active treatments will be placed in identical 60 mL syringes and labelled in a blinded manner prior to leaving the pharmacy.

5.6 Prior and Concomitant Therapy

For patients who receive study drug, any medication (including over-the-counter [OTC] medications or other investigational therapies) or therapy administered to the patient during the course of the study (starting at Screening and 14 days prior) will be recorded on the Prior and Concomitant Therapy data collection forms. The Investigator will record any AE on the AE data collection forms for which a concomitant medication/therapy was administered.

5.6.1 Prohibited Concomitant Therapy

Other inhaled vasodilators.

5.7 Investigational Product (IP) Supplies and Accountability

Investigational product supplies will not be sent to the Investigator(s) until the following documentation has been received by the Sponsor:

- Written proof of approval of the protocol and its informed consent forms (ICFs) by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for the institution where the study is to be conducted. (Due to COVID-19 and the availability of the Active study medication, the study medication will be sent to the OSU pharmacy and held in quarantine until IRB approval and the completion of Study Initiation Visit (SIV), which may be conducted remotely or in person. A NTF will be sent to OSU pharmacy instructing that the study medication not be released for use until Sponsor notification.)
- An Investigator-signed and dated FDA Form 1572.
- A signed and dated curriculum vitae of the Principal Investigator including a copy of the Principal Investigator's current medical license (required in the US) or medical registration number on curriculum vitae.

The Investigator and study staff will be responsible for the accountability of all IP supplies (dispensing, inventory, and record keeping) following Aerogen Pharma instructions and adhere to Good Clinical Practice (GCP) guidelines as well as local and/or regional requirements.

Under no circumstances will the Investigator allow the IP to be used other than as directed by this protocol. IP will not be administered to any individual who is not enrolled into the study.

An accurate and timely record of the receipt of all IP; dispensing of IP to the patient; collection of unused IP; and subsequent return of unused IP to Aerogen Pharma must be maintained. This includes, but may not be limited to: (a) documentation of receipt of IP, (b) IP dispensing log, (c) IP accountability log, (d) all shipping service receipts, and (e) documentation of returned IP to the Sponsor. All forms will be provided by Aerogen Pharma. Any comparable forms that the investigational site wishes to use must be approved by Aerogen Pharma.

The supplies and inventory records must be made available, upon request, for inspection by the designated representative of Aerogen Pharma, a representative of the FDA, or a representative of a non-US health authority. All used and unused IP are to be returned to Aerogen Pharma at the conclusion of the study.

6. CRITERIA FOR EVALUATION

6.1 Primary Endpoint

1. Reduction of respiratory failure. Failure is defined by any one of the following:

    - Requires VV ECMO
    - Inability to extubate within 10 days or reintubation within < 24 hours
    - Change in S/F, oxygenation index and P/F ratio ($\geq$15%) from baseline to 12 hours, Days 1, 2, 3, 4, 5, 6, 7, 8, 9 and Day 10 (or end of treatment)

or

1. Reduction of cardiac or circulatory failure. Failure is defined by any one of the following:

    - Need to begin inotropic therapy or 10% increase in current vasopressor therapy
    - Worsening hemodynamic parameters
    - Cardiac troponin >20% from baseline
    - BNP $\geq$ 15% of baseline
    - Need for temporary mechanical circulatory support (IABP, Impella)
    - Requires VA ECMO

6.2 Secondary Endpoints

1. Improvement in oxygenation defined as any one of the following:
    - Stabilization of PaO2/FIO2 >250
    - Improvement in FIO2 by 50% or improvements $\geq$15% in S/F, P/F ratio from baseline at 12 hours, Day 5 and Day 10 (or end of treatment)
2. Improved clinical outcomes defined as one of more of the following:
    - Time to extubation following the site's extubation protocol

- Free from re-intubation
- Reduction in ICU days
- Reduction in the number of re-admissions to the ICU due to COVID-19 within 28 days
- Reduction in total hospital days
- Mortality [28 days] defined as Cardiopulmonary mortality or mortality from all causes

3. Safety and tolerability
    - Monitoring of adverse events (AEs), serious adverse events (SAEs), chest CT or Chest X-rays, vital signs, ventilatory/oxygenation parameters, and laboratory tests.

6.3 Exploratory endpoints will include (where available):

- Change in LDH
- Change in fibrinogen
- Change in WBC count including lymphocytes and neutrophil subsets
- Change in triglycerides
- Change in ferritin
- Change in CRP / ESR
- Change in IL-6
- Change in D-Dimer

Changes in these parameters will be assessed for each patient from baseline to end of study as well as changes between the active and control groups.

6.4 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used and generally recognized as reliable, accurate, and relevant in studies of cardiac and respiratory function.

7. SAFETY ASSESSMENTS

Safety will be assessed through monitoring of adverse events (AEs) and serious adverse events (SAEs), laboratory tests, chest assessments (Chest CT or Chest X-ray), oxygenation/ventilatory parameters, and vital signs. Safety assessment frequency is shown in the Schedule of Assessments and Procedures.

7.1 General Safety Procedures

7.1.1 Vital Signs and Weight Measurements

Vital sign measurements, including systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) [beats per minute], respiratory rate (breaths per minute), and body temperature (in Celsius) will be obtained twice daily Days 1-10 or as clinically indicated. Weight (kg) will be obtained at the time of Screening and at Day 10 or end of VP treatment. Height will be obtained at the time of Screening. If unable to obtain height, the study staff will use the best reported historical height from patient or LAR.

7.1.2 Physical Examination

A physical examination will be conducted at the screening visit and will include assessments of general appearance; skin and lymphatics; eyes, ears, nose, throat; cardiovascular system; respiratory system; abdomen/gastrointestinal system; urological system; musculoskeletal and neurological systems. Other body systems may be examined as clinically indicated.

7.1.3 Laboratory Measurements

Clinical laboratory measurements to be performed are listed below. The Schedule of Assessments and Procedures shows the time points at which blood will be collected for clinical laboratory tests and pregnancy testing. The Baseline for laboratory tests is the Screening assessment.	
Category	Parameters
Hematology-CBC with diff	Hemoglobin, hematocrit, RBC, WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelets
Full Chemistry Panel	
Electrolytes	Sodium, potassium, chloride, bicarbonate, calcium
Liver function tests	AST, ALT, AP, total bilirubin
Renal function parameters	BUN, creatinine
Coagulation Studies	PT/PTT
Other	Serum or urine pregnancy test, RT-PCR for COVID-19, ESR, Troponin, BNP, fibrinogen, ferritin, LDH, Triglycerides, D-Dimer, IL-6, and CRP

7.1.4 Chest Assessments

A Chest CT or Chest X-ray will be obtained at Screening and Day 5.

7.1.5 Time Prone Protocol

The time prone protocol is a standard of care in OSU's ICU. This will be in place for all days that patients are within the ICU.

7.2 Adverse Events

7.2.1 Definitions

Adverse events are any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. For the purposes of this study, this will include unanticipated medical events in the judgment of the investigator. ***A pre-existing condition*** or symptom

is one that is present at the start of the study and is reported as part of the patient's medical history. A pre-existing condition or symptom should be reported as an AE only if its frequency, intensity or character worsens during study treatment.

All AEs that occur from the time of the first dose of study medication through the End of Study (Day 28) will be recorded and reported as Treatment-Emergent Adverse Events (TEAE). All AEs must be appropriately documented in the patient's medical chart/source documentation and on the DCFs. When known, investigators should report syndromes rather than list symptoms associated with the syndrome.

All AEs that are ongoing at the conclusion of the study should be followed until: a) resolution/stable sequelae; b) the Investigator determines that it is no longer clinically significant; or, c) the study patient is lost to follow-up. If no follow-up is provided, the Investigator must provide a written justification.

7.2.2 Adverse Events of Special Interest (AESI)

Pulmonary edema and pulmonary hemorrhage are AEs of special interest due to the mode of action of epoprostenol. If an AE of special interest occurs, the Sponsor will be notified of this occurrence within 24 hours.

7.2.3 Grading of Adverse Events

The severity of each AE will be categorized using the following criteria:

- Grade 1 (Mild): usually transient; requires no special treatment and does not interfere with the patient's daily activities.
- Grade 2 (Moderate): produces a low level of inconvenience to the patient and may interfere with daily activities. These AEs are usually ameliorated by simple therapeutic measures.
- Grade 3 (Severe): interrupts daily activity and requires systemic drug therapy or other medical treatment.

7.2.4 Relationship to Study Medication/Study Device/Procedure

The Investigator must assess the relationship of each reported AE. The Investigator must make an assessment of the relationship of the AE to the study drug/study device/procedure using the following scale:

- Unrelated: The AE is definitely not or unlikely to be associated with study medication/study device/procedure and is judged due to causes other than the study medication/study device/procedure.
- Related: The AE is possibly or probably related with study medication/study device/procedure.

7.2.5 AE Outcomes

The following terms and definitions are used in assessing the final outcome of an AE:

- Recovered/Resolved - The patient has fully recovered, or by medical or surgical treatment, the condition has returned to the level observed at the first trial-related

activity.

- Recovering/Resolving - The condition is improving and the patient is expected to recover from the event.
- Recovered/Resolved with sequelae - The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- Not recovered/Not resolved - The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known at the time of reporting.
- Fatal - This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as "recovered", "recovering", "recovered with sequelae" or "not recovered". An AE with fatal outcome must be reported as an SAE.

7.2.6 Laboratory Test and other Test Abnormalities as Adverse Events

A laboratory or other test (chest assessments, vital signs) abnormality should be reported as an AE if the Investigator considers the abnormality an AE or if the abnormality is associated with accompanying symptoms, requires medical/surgical intervention, leads to a change in study treatment, or results in discontinuation from the trial. When possible, syndromes not laboratory values, should be reported as AEs. For example, elevated hepatic transaminases associated with hepatitis should be reported as "hepatitis" and decreased hemoglobin and hematocrit requiring iron supplementation should be recorded as "anemia." Prior to reporting as an AE, abnormal tests should be repeated to verify the accuracy of the original result.

7.2.7 Serious Adverse Events

The Investigator is required to determine if each AE is a Serious Adverse Event (SAE). An SAE is any AE occurring after randomization and through Day 28 and results in any of the following outcomes:

- Death, or
- Is life-threatening, or
- Prolongation of existing hospitalization, or
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- Is a congenital anomaly/birth defect.

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

In the event of death, the cause of death should be recorded as the SAE (death is an outcome, not the AE itself).

Any planned procedures that require admission to hospital as well as any planned elective procedures (e.g., angioplasty) are not considered SAEs (unless the underlying condition has worsened or the procedure results in a worsening of the patient's condition). In addition, pregnancy that occurs during the course of the study or absence of a treatment effect will also not be considered to be an SAE and will be collected on a separate CRF.

7.2.8 Reporting for SAEs (24 Hours)

Regardless of causality, an SAE must be followed clinically until resolution or stabilization.

All SAEs after randomization and through Day 28 of the study must be reported to the Sponsor or the Sponsor's representative within 24 hours of the investigational site's knowledge of the occurrence. The investigational site will email a Serious Adverse Event Report (SAER) to the Sponsor and the Medical Monitor. Investigational sites will be provided with SAER forms. The Medical Monitor will work closely with the Sponsor to properly assess and report the SAE.

The SAE information emailed to the Sponsor or the Sponsor's representative will include the following (as available):

- Patient Number, Investigator name, and Site Number
- SAE information: event term, onset date, severity, and causal relationship
- Basic demographic information (e.g., age, gender, weight)
- The outcomes attributable to the event (death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, other important medical event[s])
- A summary of relevant test results, pertinent laboratory data, and any other relevant medical history
- The first and last dates of study drug administration.
- A statement whether study medication was discontinued or study medication administration schedule modified
- A statement whether event recurred after reintroduction of study medication if administration had been discontinued or withheld
- Supplemental anonymized information may include the following hospital records: laboratory results, radiology reports, progress notes, admission and emergency room notes, holding/observation notes, discharge summaries, autopsy reports, and death certificates

Supplemental information may be transmitted using a follow-up report and should not delay the initial report.

For regulatory purposes, initial reports of SAEs should be transmitted within the prescribed time frame as long as the following minimum information is available: patient number, suspect study medication, reporting source, and an event or outcome that can be

identified as being both serious and unexpected for which the Investigator can make a relationship assessment.

7.3 Reporting of Pregnancy

Any pregnancy where the estimated date of conception occurs either prior to the End of Study must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment. The medical monitor may decide that unblinding of the patient treatment assignment may be necessary.

An induced abortion or a spontaneous abortion is considered to be an SAE and should be reported in the same timeframe and in the same format as all other SAEs.

Pregnancies must be reported as soon as possible but no later than one business day by email.

All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but not later than 24 hours of the investigational site's knowledge of the outcome.

8. PHARMACOKINETIC ASSESSMENTS

Not applicable.

9. SCHEDULE OF ASSESSMENTS AND PROCEDURES

The assessments and procedures for this study are described in detail below and presented in the Schedule of Assessments and Procedures located behind the Synopsis.

9.1 Study Evaluation Timepoints

9.1.1 Screening (within 14 days prior to Baseline Day 1)

Potential study patients will be recruited by the study staff from patients. The following assessments will occur prior to study enrollment:

- Informed consent prior to any study procedures or assessments being performed.
- Demographic Information
- Medical History
- Physical Exam
- Prior Medication History
- Chest CT or Chest X-ray
- Inclusion/Exclusion Eligibility Assessment (including assessment of shortness of breath within the last 14 days)

- Serum/Urine Pregnancy Test (if woman of childbearing potential)
- Clinical Laboratory Sampling to include: Full Chemistry Panel including LFTs, CBC with Diff including neutrophils and lymphocytes, PT/PTT, Triglycerides, LDH, ferritin, fibrinogen, CRP, ESR, IL-6, troponin, BNP, D-Dimer, and RT-PCR for COVID-19
- Vital Signs
- Height & Weight (If height can't be obtained, use the best reported historical height)

9.1.2 Days 1-10 Treatment

9.1.2.1 Randomization

- Evaluate that the patient continues to be eligibile for the study by assessing Inclusion/Exclusion Criteria.
- Once eligibility has been confirmed, a Subject number beginning with 101 and rising sequentially will be assigned to the next enrolled subject.
- A blinded order for the Investigational Drug Services group will be generated by EPIC for the next sequential subject to be randomized.
- The unblinded pharmacist will prepare the treatment assignment (Active or Control) for the next assigned Subject number.
- The reconstituted study drug will be protected from light and labelled in a blinded manner to ensure maintenance of the study blind.
- Subjects will be randomized to receive either Active or Control for a maximum of 10 days, as clinically indicated and at the discretion of the Investigator.

9.1.2.2 Baseline-Day 1 (0 Hour)

- Continue evaluation eligibility by assessing Inclusion/Exclusion Criteria.
- Study drug treatment will begin at a starting dose of 13.6 ng/kg/min based on the concentration used to calculate Active treatment in mL/hr and can be titrated up to 30.6 ng/kg/min or down to 3.4 ng/kg/min as clinically warranted. The B.Braun syringe pump will be set to the appropriate dose in mL/hr utilizing the subject's sex and height (ideal body weight).
- Vital signs will be assessed twice daily in AM and PM while on study drug. Efforts will be made to obtain vital signs at the same time each day. Vital signs include: temperature, pulse rate, respiration rate and blood pressure.
- Adverse Event/SAE assessment daily
- Concomitant medication evaluation daily
- Continuous pulse oximetry (SpO_2)
- Ventilatory parameters assessed twice daily while on study drug: Ventilator Type, Vent Mode, FiO_2, Inspiratory time, Mean Airway Pressure, Peak Inspiratory Pressure, Positive End Expiratory Pressure, Tidal Volume, and Respiratory Rate
- Time Prone Position-16 hours per day per OSU Protocol

9.1.2.3 Day 1-12 hours

- Clinical Laboratory Sampling to include: Full Chemistry Panel including LFTs, CBC with Diff including neutrophils and lymphocytes, PT/PTT, Triglycerides, LDH, ferritin, fibrinogen, CRP, ESR, IL-6, troponin, BNP, and D-Dimer.
- Continue to administer study drug if clinically indicated.
- Adverse Event/SAE assessment daily
- Concomitant medication evaluation daily
- Oxygenation measurement via continuous pulse oximetry (SpO_2)
- Ventilatory parameters assessed twice daily while on study drug: Ventilator Type, Vent Mode, FiO_2, Inspiratory time, Mean Airway Pressure, Peak Inspiratory Pressure, Positive End Expiratory Pressure, Tidal Volume, and Respiratory Rate
- Vital signs will be assessed twice daily in AM and PM. Efforts will be made to obtain vital signs at the same time each day. Vital signs include: temperature, pulse rate, and blood pressure.
- Time Prone Position-16 hours per day per OSU Protocol

9.1.2.4 Days 2-10 (While on study drug)

- Continue to administer study drug if clinically indicated.
- Adverse Event/SAE assessment daily
- Concomitant medication evaluation daily
- Oxygenation measurement via continuous pulse oximetry (SpO_2)
- Ventilatory parameters assessed twice daily: Ventilator Type, Vent Mode, FiO_2, Inspiratory time, Mean Airway Pressure, Peak Inspiratory Pressure, Positive End Expiratory Pressure, Tidal Volume, and Respiratory Rate
- Vital signs will be assessed twice daily in AM and PM. Efforts will be made to obtain vital signs at the same time each day. Vital signs include: temperature, pulse rate, and blood pressure.
- Time Prone Position-16 hours per day per OSU Protocol
- Full Chemistry Panel including LFTs, CBC with Diff including neutrophils and lymphocytes, PT/PTT and RT-PCR for COVID-19. (Day 5 only)
- Chest CT or Chest X-ray (Day 5 only)

- Full Chemistry Panel including LFTs, CBC with Diff including neutrophils and lymphocytes, PT/PTT, Triglycerides, LDH, ferritin, fibrinogen, CRP, ESR, IL-6, troponin, BNP, D-Dimer, and RT-PCR for COVID-19 (Day 10 only).

- Obtain weight. (Day 10 only or at end of study drug dosing)

9.1.2.5 Weaning

See Section 5.3.4 and Table 3 for weaning guidelines.

9.1.3 Day 28/End of Study (EOS)

- Assess AEs/SAEs
- Assess Mortality
- Assess concomitant medications

9.2 Data Collection

Investigator or designee will enter the information required by the protocol onto source documents and enter data into data collection forms (DCFs) in an excel spreadsheet provided by Aerogen Pharma.

9.3 Clinical Data Management

Data from source documents will be verified against the DCF and any discrepancies will be clarified and resolved with study staff.

9.4 Database Quality Assurance

All data will be remotely monitored by the Sponsor due to the COVID-19 pandemic. Should restrictions be lifted at OSU, an on-site visit may occur if all parties are in agreement.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Methods

A Statistical Analysis Plan will be not be developed as this is an exploratory trial. Any statistical evaluation will be handled internally by Aerogen Pharma or their designee.

10.2 Determination of Sample Size

The number of patients has been selected to enable an adequate clinical assessment of pharmacodynamics, safety, and tolerability parameters without presenting undue risk to a large number of patient's being exposed to this investigational product.

10.3 Analyses Sets

All patients who are enrolled in the study and who receive at least one dose of study drug will be included in the intent-to-treat (ITT) analyses of pharmacodynamic and safety data. All available data will be used and missing data will not be estimated or carried forward

in any statistical summary or analyses.

Descriptive summary statistics include the number of patients, mean, median, percent coefficient of variation (% CV) (if required), standard deviation, and minimum and maximum values (quantitative variables) or the number of patients and percentages by category (qualitative variables). Changes will be assessed as the difference between baseline measurements and the appropriate post-dose measurements unless otherwise specified. Mean differences between active and control groups (when available) will be assessed and significance will be determined on the basis of a 95% CI. Individual patient listings of data will also be provided to allow for review of all pharmacodynamic, safety, and tolerability parameters.

10.4 Randomization

Patients will be randomized 1:1. A randomization schedule will be provided to the unblinded pharmacist. Should unblinding be requested due to a medical emergency, the unblinded pharmacist will work with the medical monitor or Sponsor unblinded CRA to obtain the required information.

10.5 Demographic and Other Baseline Characteristics

Continuous demographic and other baseline characteristics (such as age, weight, and height) will be summarized using n, mean, SD, median, minimum, and maximum. Qualitative characteristics (such as gender and race) will be summarized by counts and percentages.

10.6 Criteria for Evaluation

10.6.1 Primary Efficacy Endpoint

The primary efficacy endpoint:

1. Reduction of respiratory failure. Failure is defined by any one of the following:

    - Requires VV ECMO
    - Inability to extubate patient within 10 days or reintubation within <24 hours
    - Change in S/F, oxygenation index and P/F ratio ($\geq$15%) from baseline to 12 hours, Days 1, 2, 3, 4, 5, 6, 7, 8, 9 and Day 10 (or end of treatment)

or

2. Reduction of cardiac or circulatory failure. Failure is defined by any one of the following:

    - Need to begin inotropic therapy or 10% increase in current vasopressor therapy
    - Worsening hemodynamic parameters
    - Cardiac troponin >20 % from baseline
    - BNP $\geq$ 15% of baseline

- Need for temporary mechanical circulatory support (IABP, Impella)
- Requires VA ECMO

10.6.2 Secondary Efficacy Endpoints

Key secondary endpoints include:

1. Improvement in oxygenation defined as any one of the following:
   - Stabilization of PaO2/FIO2 >250
   - Improvement in FIO2 by 50% or improvements ≥15% in S/F, P/F ratio from baseline at 12 hours, Day 5 and Day 10 (or end of treatment)
2. Improved clinical outcomes defined as one of more of the following:
   - Time to extubation following the site's extubation protocol
   - Free from reintubation
   - Reduction in ICU days
   - Reduction in the number of re-admissions to the ICU due to COVID-19 within 28 days
   - Reduction in total hospital days
   - Mortality [28 days] defined as Cardiopulmonary mortality or mortality from all causes
3. Safety
   - Monitoring of adverse events (AEs), serious adverse events (SAEs), chest CT or Chest X-rays, vital signs, ventilatory/oxygenation parameters, and laboratory tests.

10.6.3 Key Exploratory Endpoints include:

- Change in LDH
- Change in fibrinogen
- Change in WBC count including lymphocytes and neutrophil subsets
- Change in triglycerides
- Change in ferritin
- Change in CRP / ESR
- Change in IL-6
- Change in D-Dimer

Changes in these parameters will be assessed for each patient from baseline to end of study as well as changes between the active and control groups.

10.7 Extent of Exposure

Exposure data will be summarized by using frequencies and percentages.

10.8 Safety Analyses

Safety measurements include AE/SAEs, vital signs, chest assessments (Chest CT or Chest X-ray), laboratory tests, and oxygenation/ventilatory parameters. Safety data will be summarized by using frequencies and incidence rates.

10.8.1 Adverse Events

AEs will be classified into standardized medical terminology from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be presented by preferred term nested within System Organ Class. Verbatim description and all MedDRA level terms, including the lower level terms, for all AEs will be contained in the data listings of the clinical study report (CSR).

AEs will be summarized by presenting the incidence of AEs. Although a MedDRA term may be reported more than once for a patient, that patient will be counted only one time in the incidence count for that MedDRA term.

Treatment-emergent adverse events (TEAEs) will be analyzed. AEs that are not treatment-emergent will be listed. A TEAE is defined as

- AEs that emerge during treatment, having been absent at pretreatment, or
- Reemerge during treatment, having been present at pretreatment but stopped prior to treatment, or
- Worsen in severity or frequency during treatment relative to the pretreatment state, when the AE is continuous.

Adverse events of special interest (AESI) will be analyzed. An AESI is defined as:

- Serious or non-serious adverse that is one of scientific and medical concern specific to the sponsor's product for which ongoing monitoring and rapid communication by the investigator to the sponsor is required
- Events or symptoms thought to potentially be associated with the investigational compound, device, or disease under study, or
- Can arise with any use of a drug/device (e.g. off-label use, use in combination with another approved drug), with any route of administration, formulation, or dose, including an overdose.

10.8.2 Laboratory Values

Clinical laboratory results post-Baseline will be evaluated for markedly abnormal values. For the incidence of markedly abnormal laboratory values, each patient may be counted once in the laboratory parameter value high and in the laboratory parameter low categories as applicable. Descriptive summary statistics (e.g. mean, SD, median, minimum, maximum) for laboratory values and changes from baseline will be evaluated.

10.8.3 Vital Signs

Vital sign values will be evaluated on an individual basis by patient. Abnormal vital sign values will be identified as those outside (above or below) the reference range. Descriptive summary statistics (e.g., mean, SD, median, minimum, maximum) for vital sign parameters and changes from Baseline will be evaluated.

10.9 The Procedure for Revising the Statistical Analysis Plan

Not Applicable.

11. ADMINISTRATIVE PROCEDURES AND INSTRUCTIONS

11.1 Ethics

11.1.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an IRB or IEC constituted and functioning in accordance with International Conference on Harmonization (ICH) E6, Section 3, and any local regulations, i.e., Federal Regulations, Title 21 Code of Federal Regulations (CFR) Part 56. Any protocol amendment and/or revision to the ICF will be resubmitted to the IRB/IEC for review and approval (except for changes involving only logistical or administrative aspects of the study (e.g., change in CRA[s], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

A signed letter of study approval from the IRB/IEC Chairman must be sent to the Principal Investigator with a copy to the Sponsor prior to study start. If the IRB/IEC decides to suspend or terminate the study, the Investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the Sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the Investigator or Sponsor, depending on local regulatory obligations. If the Investigator is required to report to the IRB/IEC, he/she will forward a copy to the Sponsor at the time of each periodic report. The Investigator or the Sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable AEs per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the Investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

11.1.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating practices of Aerogen Pharma (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- ICH - E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonization of Pharmaceuticals for Human Use.

- US CFR dealing with clinical studies (21 CFR, including parts 50 and 56 concerning Informed Patient Consent and IRB regulations).

11.1.3 Patient Information and Informed Consent

As part of administering the informed consent document, the Investigator must explain to each patient or their legally authorized representative (LAR), the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, and currently available alternative treatments. Each patient must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The patient or their LAR should understand the statement before signing and dating it and will be given a copy of the signed document. The patient or their LAR will be asked to sign an informed consent prior to any study-specific procedures being performed. No patient can enter the study before his/her informed consent has been obtained. Due to the COVID-19 pandemic and restrictions on hospital visitors, informed consent may be obtained via telephone or video conference call if the patient is incapacitated or sedated due to the severity of their illness. A witness for the study team should be present when a call or video conference is occurring with the patient's LAR. This process should be carefully documented in the subject's medical records.

An unsigned copy of an IRB/IEC and Sponsor-approved written informed consent must be prepared in accordance with ICH E 6, Section 4, and all applicable local regulations, i.e., Federal Regulations, Title 21, CFR Part 50, and provided to the Sponsor. Each patient or their LAR must sign (or give verbal consent with study staff witnessing the verbal consent) an approved informed consent prior to study participation. The form must be signed and dated by the appropriate parties. The original signed ICF for each patient will be verified by the Sponsor and kept in the study center's investigational site files.

The patient should be informed in a timely manner if new information becomes available that might be relevant to the patient's willingness to continue participation in the trial. The communication of this information should be documented.

11.2 Administrative Procedures

11.2.1 Changes to the Protocol

There are to be no changes to the protocol without written approval from the Sponsor. Protocols will be followed as written.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of patients, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRBs/IECs of all investigational sites and, as required, by the regulatory authority. These requirements

should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all patients included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary for safety reasons, the Medical Monitor must be notified promptly and the IRB/IEC for the site must be informed as soon as possible.

Changes affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval, but the IRB/IEC must be kept informed of such changes. In these cases, the Sponsor will send a letter to the site for forwarding on to the IRB/IEC detailing such changes.

11.2.2 Adherence to the Protocol

The Investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.2.3 Monitoring Procedures

The Sponsor or Sponsor's representative will maintain contact with the Investigator and designated staff by telephone, letter, and/or email between study visits. Monitoring visits to each investigational site will be conducted by the sponsor either remotely or in person.

In accordance with ICH E6, Section 6.10, source documents include, but are not limited to the following:

- Clinic, office, hospital charts.
- Copies or transcribed health care provider notes which have been certified for accuracy after production.
- Recorded data from automated instruments such as mechanical ventilators, x-rays, and other imaging reports, e.g., sonograms, computed tomography scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, electroencephalographs, polysomnography, pulmonary function tests (regardless of how these images are stored, including microfiche and photographic negatives).
- Records of telephone contacts.
- Diaries or evaluation checklists.
- Investigational product distribution and accountability logs maintained in pharmacies or by research personnel.
- Laboratory results and other laboratory test outputs, e.g., serum pregnancy test result documentation.
- Correspondence regarding a study patient's treatment between physicians or memoranda sent to the IRBs/IECs.
- CRF components (e.g., questionnaires) that are completed directly by patients and serve as their own source.

11.2.4 Recording of Data

In order to provide the Sponsor with accurate, complete, and legible records following criteria are to be maintained. The Investigator will enter the information required by the protocol onto the data collection forms (DCFs) provided by the sponsor as agreed upon with the research staff.

11.2.5 Data Storage and Retention of Records

The circumstances of completion or termination of the study notwithstanding, the Investigator has the responsibility to retain all study documents, including but not limited to the protocol, copies of data collection forms (DCFs) , Investigator's Brochure, regulatory agency registration documents, e.g., FDA 1572 form, ICFs, and IRB/IEC correspondence. The investigational site should plan on retaining study documents as follows:

- For at least two years following the date a marketing application is approved for the investigational product for the indication for which it is being investigated, or
- Until two years after the investigation is formally discontinued and no application is to be filed or if the application is not approved.

It is requested that at the completion of the required retention period, or should the Investigator retire or relocate, the Investigator contacts the Sponsor, allowing the Sponsor the option of permanently retaining the study records.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Data will be coded (de-identified), stored in a secure electronic database during and after the study, and will not be shared with unauthorized persons. The principal investigator and co-investigator will have access to the data to review and analyze the data, as described in this protocol. For the protection and privacy of the patients, no identifying information will be released. Data will be retained and possibly used in the future for further analysis. All identifiers will be removed and not be shared at any time.

11.2.6 Handling of Investigational Product

Investigational study drug (Flolan) will be inventoried and maintained within the site's Investigational Drug Services . It will be stored according to their protocols and procedures. The study drug should not be dispensed to patients in the VentaProst COVID trial (APC-VPCOV-CLN-001) until a favorable IRB approval has been obtained by the OSU IRB and a study initiation visit has been conducted by the Sponsor. Investigational device supplies must be kept in an appropriate secure area (e.g., locked cabinet) and stored according to the conditions specified on the investigational product labels. The Investigator (or designated pharmacist) must maintain an accurate record of the shipment and dispensing of the IP (both device and drug) in an IP accountability log, a copy of which must be given to the Sponsor at the end of the study. An accurate record of the date and amount of IP dispensed to each patient must be available for inspection at any time. The assigned sponsor representative will review these documents along with all other study conduct documents at an appropriate interval of visit to the investigational

site once IP has been received by the investigational site. Due to COVID-19 a physical inventory of IP (drug and device supplies) may not be possible. If at all possible, an inventory of supplies should be conducted via video conferencing. If video conferencing is not possible, study staff will inventory supplies and provide documentation to Aerogen Pharma.

All IP supplies (with the exception of OSU stock 0.9% sodium chloride solution supplies) are to be used only for this protocol and not for any other purpose. The Investigator (or designated pharmacist) must not destroy any IP product labels or any partly used or unused IP supply without Sponsor authorization. At the conclusion of the study and as appropriate during the course of the study, the Investigator (or designated pharmacist) will return or properly dispose of all used IP. Unused investigational device and drug components will be returned to Aerogen Pharma at the conclusion of the study.

11.2.7 Publication of Results

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each Investigator and Aerogen Pharma, as appropriate.

11.2.8 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the course of this study will be kept confidential by the Investigator, the Investigator's staff, and IRB/IEC and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study without the written consent of the Sponsor. No data collected as part of this study will be utilized in any written work, including publications, without the written consent of Sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in the Confidentiality Agreement between the Sponsor and the Investigator. All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Confidentiality Agreement between the Investigator and Sponsor (provided by the Sponsor).

11.2.9 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time.

The Investigator reserves the right to discontinue the study should his/her judgment so dictate. If the Investigator terminates or suspends a trial without prior agreement of the Sponsor, the Investigator should inform the Institution where applicable, and the Investigator/Institution should promptly inform the Sponsor and the IRB/IEC and should provide the Sponsor and the IRB/IEC a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.2.10 Patient Insurance and Indemnity

The Sponsor will provide the insurance in accordance with local guidelines and requirements as a minimum for the patients participating in this study.

12. REFERENCES

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PROTOCOL TITLE	**TITLE: DOUBLE-BLIND, PLACEBO CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF VENTAPROST (INHALED EPOPROSTENOL DELIVERED VIA DEDICATED DELIVERY SYSTEM) IN SUBJECTS WITH COVID-19 REQUIRING MECHANICAL VENTILATION**
PROTOCOL NUMBER	APC-VPCOV-CLN-001
INVESTIGATIONAL PRODUCT	VentaProst™
INDICATION	Reduction of respiratory, cardiac or circulatory failure in patients with COVID-19
PHASE	Phase 2a
SPONSOR	Aerogen Pharma Limited 1660 S Amphlett Boulevard, Suite 360 San Mateo, CA 94402 United States
MEDICAL MONITOR	Matthew Exline, MD
AMENDMENT #2 APPROVAL DATE	03 November 2020
GCP STATEMENT	This study is to be performed in full compliance with International Conference on Harmonization (ICH) and all applicable local Good Clinical Practices (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
CONFIDENTIALITY STATEMENT	This document is confidential as it contains proprietary information of Aerogen Pharma. Any viewing or disclosure of such information that is not authorized in writing by the Aerogen Pharma is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

SPONSOR PROTOCOL APPROVAL PAGE

PROTOCOL TITLE	**A DOUBLE-BLIND, PLACEBO CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF VENTAPROST (INHALED EPOPROSTENOL DELIVERED VIA DEDICATED DELIVERY SYSTEM) IN SUBJECTS WITH COVID-19 REQUIRING MECHANICAL VENTILATION**
PROTOCOL NUMBER	**APC-VPCOV-CLN-001**
AMENDMENT #1 APPROVAL DATE	**03 November 2020**

04Nov2020

Judy Doto, RN, BSN — Date
Head of Clinical Operations
Aerogen Pharma

04 NOV 2020

Jim Fink PhD, RRT, FCCP — Date
Chief Scientific Officer
Aerogen Pharma

04 NOV 2020

Plamena Entcheva-Dimitrov, PhD, RAC — Date
Head of Regulatory and Medical Affairs
Aerogen Pharma

Andy clark 06 Nov 2020

Andy Clark PhD — Date
Vice President and General Manager
Aerogen Pharma

INVESTIGATOR'S SIGNATURE PAGE

PROTOCOL TITLE	**A DOUBLE-BLIND, PLACEBO CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF VENTAPROST (INHALED EPOPROSTENOL DELIVERED VIA DEDICATED DELIVERY SYSTEM) IN SUBJECTS WITH COVID-19 REQUIRING MECHANICAL VENTILATION**
PROTOCOL NUMBER	**APC-VPCOV-CLN-001**
AMENDMENT #1 APPROVAL DATE	**03 November2020**

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with ICH-GCPs and all applicable local guidelines.

_____

Principal Investigator (printed/typed)

_____

Principal Investigator Signature Date

1. CLINICAL PROTOCOL SYNOPSIS

Sponsor	Aerogen Pharma
Protocol No.	APC-VPCOV-CLN-001
Title of Study	Double-blind, placebo controlled study to assess the efficacy and safety of VentaProst (Inhaled epoprostenol delivered via dedicated delivery system) in subjects with COVID-19 requiring mechanical ventilation.
Study Centers	One clinical site in the US
Phase	Phase 2a
Objectives	**Primary Objective:** The primary objective of this study is the reduction of respiratory, cardiac or circulatory failure in patients with confirmed COVID-19. **Secondary Objectives:** The secondary objective in this study is to evaluate the effects of VentaProst on improvement in oxygenation and improvement in clinical outcomes. The study will also evaluate the effects of VentaProst on inflammatory parameters in subjects with confirmed COVID-19.
Study Design	This is a double-blind, placebo controlled study of VentaProst (Active) as compared to placebo (Control). Active is inhaled epoprostenol administered via the VentaProst delivery system in 10 COVID-19 positive patients. Control is inhaled 0.9% sodium chloride solution administered via the VentaProst delivery system in 10 COVID-19 positive patients. Throughout the remainder of the protocol both Active and Control will be referred to as "study drug". This study will evaluate the potential therapeutic benefit of VentaProst in treating patients with COVID-19 who require mechanical ventilation and are at risk for the progression of respiratory and/ or cardiac/circulatory failure. This study will assess the efficacy and safety of VentaProst at an initial dose of 13.6 ng/kg/min (A range from 3.4-30.6 ng/kg/min may be administered as clinically required for a maximum of 10 days at the discretion of the Investigator. Patients will be followed through Day 28 to assess clinical outcomes. Patients will be consented and randomized to either the Active or Control group within 48 hours of being placed on a mechanical ventilator. Patients will be administered study drug using the VentaProst delivery system which allows up and down titration of study drug to achieve hemodynamic and oxygenation stability. The starting dose of study drug will be initiated at 13.6 ng/kg/min. Based on hemodynamic and oxygenation parameters, the dose of study drug can be increased in 3.4 ng/kg/min increments up to a maximum of 30.6 ng/kg/min or down to a minimum of 3.4 ng/kg/min. Study drug will be administered based on the pump rate calculated for active treatment in mL/hr. The titration table below (Table 1) shows the typical up and down titration steps for study drug.

<table>
<tr><td></td><td>

Table 1: Overview of Titration and Weaning Guidelines

Up titration Guideline*	Downward Titration / Weaning Guideline**
Start Dose: 13.6 ng/kg/min 1st Step Up Dose (17.0) 2nd Step Up Dose (20.4) 3rd Step Up Dose (23.8) 4th Step Up Dose (27.2) 5th Step Up Dose (30.6)	Start Dose: 13.6 ng/kg/min 1st Step Down dose (10.2) 2nd Step Down Dose (6.8) 3rd Step Down dose (3.4)

* The study drug will be administered based on the pump rate calculated for active treatment in mL/hr.**If the patient has been up-titrated weaning should occur from that level in 3.4 ng/kg/min decrements.

Patients will be weaned from study drug slowly to avoid rebound vasoconstriction. During weaning, doses will be decreased in steps of 3.4 ng/kg/min increments, with a minimum of 15 minutes between changes. The weaning process should occur in isolation to other treatment changes (no changes in inotropes, vasopressors, or vasodilators) whenever possible. Patients will be observed closely before, during, and after dose changes. In the event patients demonstrate signs of hemodynamic instability or a decrease in oxygenation indicated by pulse oximetry during downward titration, the dose will be returned to its previous level. Once patients have been stable for at least 15 minutes, repeat attempts at dose reduction may be undertaken. The process will continue until patients are fully weaned. Patients will be monitored for safety and efficacy throughout study drug administration.

</td></tr>
<tr><td>Number/Type of Patients</td><td>

Approximately 20 COVID-19 positive patients requiring mechanical ventilation will be enrolled in this study.

Patients will be randomized to either VentaProst Active (aerosolized epoprostenol administered via the VentaProst delivery system) or VentaProst Control (aerosolized 0.9% sodium chloride solution administered via the VentaProst delivery system).

</td></tr>
<tr><td>Inclusion Criteria</td><td>

Patients are eligible for this study if they meet all of the following criteria:

1. Women and Men Age ≥18 years old (no upper limit)
2. Confirmed COVID-19 positive by RT-PCR test
3. Patients who require invasive mechanical ventilation.
4. Enrolled into study within 48 hours of being placed on mechanical ventilation
5. Consent or professional consent obtained
6. Duration of shortness of breath must be within the previous 14 days.
7. Female subjects of childbearing potential must have a negative pre-treatment pregnancy test (serum or urine).
8. Received or currently receiving dexamethasone for the treatment of COVID.
9. Willing and able to comply with treatment schedule and follow-up.

</td></tr>
</table>

Exclusion Criteria	Patients are **NOT** eligible for this study if they meet any of the following criteria: 1. Patients on ECMO support. 2. Patients receiving another inhalation research medication or inhaled nitric oxide. 3. Not expected to survive for 48 hours. 4. Pregnant (positive pregnancy test in a pre-dose examination) or breastfeeding 5. Open tracheostomy. 6. Clinical contra-indication, as deemed by the attending physician. 7. Allergy to Epoprostenol and its diluent 8. Using inhaled vasodilators at baseline. 9. Patients who are hemodynamically unstable as determined by investigator 10. Patients with significant hemoptysis as determined by investigator
Study Treatment(s)	Patients will receive study drug via mechanical ventilator, starting at 13.6 ng/kg/min. If determined by the treating physician, study drug can be up titrated in 3.4 ng/kg/min increments to a maximum of 30.6 ng/kg/min or down to a minimum of 3.4 ng/kg/min. At the Investigator's discretion, the patient will be weaned off the drug in 3.4 ng/kg/min increments. Study drug will be administered based on the pump rate calculated for active treatment in mL/hr. Study drug can be administered up to 10 days.
Duration of Treatment	The duration of study participation for each patient is as follows: • Screening: up to 14 days • Treatment: up to 10 days • Follow up: 28 days
Criteria for Evaluation	<u>Primary Endpoint</u> 1. Reduction of respiratory failure. Failure is defined by any one of the following: • Requires VV ECMO • Inability to extubate patient within 10 days or reintubation within < 24 hours • Change in S/F, oxygenation index and P/F ratio (≥15%) from baseline to 12 hours, Days 1, 2, 3, 4, 5, 6, 7, 8, 9 and Day 10 (or end of treatment) **or** 2. Reduction of cardiac or circulatory failure. Failure is defined by any one of the following: • Need to begin inotropic therapy or 10% increase in current vasopressor therapy • Worsening hemodynamic parameters • Cardiac troponin > 20% from baseline • BNP ≥ 15% of baseline • Need for temporary mechanical circulatory support (IABP, Impella) • Requires VA ECMO <u>Secondary Endpoints:</u> 1. Improvement in oxygenation defined as any one of the following: • Stabilization of PaO2/FIO2 >250 • Improvement in FIO2 by 50% or improvements <u>≥</u>15% in S/F, P/F ratio from baseline at 12 hours, Day 5 and Day 10 (or end of treatment)

	2. Improved clinical outcomes defined as one of more of the following: • Shorter time to extubation following the site's extubation protocol • Free from reintubation • Reduction in ICU days • Reduction in the number of re-admissions to the ICU due to COVID-19 within 28 days. • Reduction in hospital days Mortality (28 Days) defined as Cardiopulmonary mortality or mortality from all causes. 3. Safety and tolerability: • Monitoring of adverse events (AEs), serious adverse events (SAEs), chest CT or Chest X-rays, vital signs, ventilatory and oxygenation parameters, and laboratory tests. **Exploratory endpoints will include (where available):** 1. Change in LDH 2. Change in fibrinogen 3. Change in WBC count including lymphocytes and neutrophil subsets 4. Change in triglycerides 5. Change in ferritin 6. Change in CRP / ESR 7. Change in IL-6 8. Change in D-Dimer Changes in these parameters will be assessed for each patient from baseline to end of study as well as changes between the active and control groups.
Ventilatory Parameters	<u>OSU SOC:</u> Ventilator Type (GE) Parameters to monitor are: 1. Ventilator Mode 2. FiO_2 3. Inspiratory Time 4. Mean Airway Pressure 5. Peak Inspiratory Pressure 6. Positive End Expiratory Pressure 7. Respiratory Rate 8. Tidal Volume
Criteria for Stopping VentaProst Treatment	**<u>Individual patients stopping criteria:</u>** At any time during study drug administration, patients may be removed from study treatment and placed on standard of care (SoC) therapy if they meet one or more of the following pre-defined criteria leading to a deterioration in their condition: • Severe hypotension as evidenced by a systolic BP < 90 mmHg or MAP < 60 mmHG for >2 hours from the start of VentaProst • Need for VV ECMO • Need to increase existing vasopressor therapy by more than 25%

	• Worsening in oxygenation, ventilatory, or hemodynamic parameters that in the opinion of the investigator the patient should be removed from study treatment • Massive hemoptysis thought to be clinically significant and not related to endotracheal tube trauma • Pulmonary edema • If a clinically inadequate response to treatment is observed **Study stopping criteria:** If 3 patients are removed from the study for any of the above conditions, the study will stop further enrollment and an investigation will be conducted to determine the cause of the events. An independent safety evaluation will also be conducted. If it is suspected that the investigational product has caused the events, the study will be terminated. **Independent Safety Evaluation:** Independent safety evaluation will be conducted by a licensed physician who is not involved in the VentaProst COVID-19 clinical study or the sponsoring organization.
Statistical Methods	All patients who are enrolled in the study and who receive at least one dose of study drug will be included in the intent-to-treat (ITT) analyses of pharmacodynamic and safety data. All available data will be used and missing data will not be estimated or carried forward in any statistical summary or analyses. Descriptive summary statistics include the number of patients, mean, median, percent coefficient of variation (% CV) (if required), standard deviation, and minimum and maximum values (quantitative variables) or the number of patients and percentages by category (qualitative variables). Changes will be assessed as the difference between baseline measurements and the appropriate post-dose measurements unless otherwise specified. Mean differences between active and historical control groups will be assessed and significance will be determined on the basis of a 95% CI. No formal estimate of the sample size has been made. This is an exploratory study and the number of patients was selected to enable an adequate clinical assessment of pharmacodynamic, safety, and tolerability parameters without presenting undue risk to a large number of patients.
Efficacy Analysis	Efficacy will be secondarily determined by summarizing success or failure to meet any of the primary or secondary endpoints as compared to Control treatment.
Safety Analyses	Safety data will be summarized for both treatment groups including frequencies and incidence rates. Safety will be assessed through monitoring of adverse events (AEs), serious adverse events (SAEs), chest CTs or chest X-rays, laboratory tests, oxygenation and ventilatory parameters, and vital signs.

Table 2: Schedule of Assessments and Procedures

	Screening	VentaProst - Day 1		VentaProst Days 2-10									End of Study
Study Procedures	**Within 14 Days Prior to Baseline**	**Baseline - 0 Hr**	**12 hrs**	**D-2**	**D-3**	**D-4**	**D-5**	**D-6**	**D-7**	**D-8**	**D-9**	**D-10**	**Day 28 (+/- 2 days)**
Written Informed Consent	X												
Demographics	X												
Medical History	X												
Review Inclusion/Exclusion Eligibility Criteria	X	X											
Medication History/ Prior Meds	X												
Physical Examination	X												
Weight/Height[1]	X											X	
Randomization		X											
Chest CT Scan or CXR	X						X						
Clinical Laboratory Sampling[2]	X		X				X					X	
Pregnancy Test (Serum or Urine)	X												
RT-PCR + for COVID-19	X						X					X	
Administer VentaProst		X	X	X	X	X	X	X	X	X	X	X	
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	
Oxygenation Measurements[4]		X	X	X	X	X	X	X	X	X	X	X	
Ventilator Parameters[5]		X	X	X	X	X	X	X	X	X	X	X	
AE/SAE Monitoring		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X
Prone position		X	X	X	X	X	X	X	X	X	X	X	

[1] Height only performed at screening

[2] Clinical Labs include: Safety labs: CBC (lymphocyte and neutrophil counts), Full Chemistry Panel (including LFTs) and PT/PTT drawn Screening, Day 1-12 hours, Days 5 & 10. Triglycerides, LDH, ferritin, fibrinogen, CRP, ESR, IL-6, D-Dimer, troponin, BNP drawn at Screening, Day 1-12 hours and D-10.

[3] Vital signs: Prior to initiating VentaProst, Days 1-10 twice daily (morning and evening) at the same time to reduce exposure to Health Care Professionals to include; temperature, pulse rate, blood pressure.

[4] Continuous SpO2 via pulse oximetry

[5] Ventilator Parameters will be collected twice daily along with vital signs and include: Ventilator Type, Ventilator Mode, FiO_2, Inspiratory Time, Mean Airway Pressure, Peak Inspiratory Pressure, Positive End Expiratory Pressure, Tidal Volume and Respiratory Rate

[6] Time Prone Position – 16 hours per day per OSU protocol

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LIST OF ACRONYMS, ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
Active	Inhaled epoprostenol administered via the VentaProst delivery system
AE	Adverse |Event
ALI	Acute Lung Injury
ALT (SGPT)	Alanine Aminotransferase (serum glutamic pyruvic transaminase)
AP	Alkaline Phosphatase
ARDS	Acute Respiratory Distress Syndrome
AST (SGOT)	Aspartate Aminotransferase (serum glutamic oxaloacetic transaminase)
bpm	Beats Per Minute
BNP	Brain Natriuretic Peptide
BUN	Blood Urea Nitrogen
cAMP	Cyclic Adenosine Monophosphate
CI	Cardiac Index (L/min/m^2)
CO	Cardiac Output (L/min)
Control	Inhaled 0.9% sodium chloride solution, USP administered via the VentaProst delivery system
CFR	Code of Federal Regulations
C_{max}	Maximum Concentration
CPB	Cardiopulmonary Bypass
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-Reactive Protein
CSR	Clinical Study Report
CNTS	Continuous Nebulization Tube Set
CVP	Central Venous Pressure (mm Hg)
DCF	Data Collection Form

Abbreviation	Term
DNR	Do Not Resuscitate
dPAP	Diastolic Pulmonary Arterial Pressure (mm Hg)
dSAP	Diastolic Systemic Arterial Pressure (mm Hg)
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
ESR	Erythrocyte Sedimentation Rate
ETT	Endotracheal Tube
FDA	Food and Drug Administration
FiO_2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
HME	Heat-Moisture Exchanger
HR	Heart Rate (bpm)
IABP	Intra-aortic Balloon Pump
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IL-6	Interleukin 6
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
LAR	Legally Authorized Representative
LDR	Lung Dosing Rate
LFT	Liver Function Test
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute
mPAP	Mean Pulmonary Arterial Pressure (mm Hg)
mSAP	Mean Systemic Arterial Pressure (mm Hg)
NC	Nasal Cannula
ng	Nanogram
OR	Operating Room
OTC	Over-the-Counter
PAH	Pulmonary Arterial Hypertension
PaO_2	Partial Pressure of Oxygen in Arterial Blood
PAP	Pulmonary Arterial Pressure (mm Hg)
PCWP	Pulmonary Capillary Wedge Pressure
PD	Pharmacodynamic
PEEP	Positive End Expiratory Pressure
PH	Pulmonary Hypertension
PIP	Peak Inspiratory Pressure
PK	Pharmacokinetic
PP	Per Protocol

Abbreviation	Term
PGI_2	Prostaglandin I_2 (epoprostenol)
PVR	Pulmonary Vascular Resistance (dyn/sec/cm^5)
RBC	Red Blood Cell (count)
RH	Right Heart
RHF	Right Heart Failure
RT-PCR	Reverse Transcription Polymerase Chain Reaction
RVSWI	Right Ventricular Stroke Work Index
SAE	Serious Adverse Event
SaO_2	Arterial Oxygen Saturation
sPAP	Systolic Pulmonary Arterial Pressure (mm Hg)
sSAP	Systolic Systemic Arterial Pressure (mm Hg)
SE	Standard Error
SOP	Standard Operating Procedures
SOC	Standard of Care
SpO_2	Oxygen Saturation by Pulse Oximetry
Study Drug	Active or Control Treatment
SVR	Systemic Vascular Resistance
TEAE	Treatment-Emergent Adverse Event
TEE	Transesophageal Echocardiogram
TPG	Transpulmonary Gradient
$t_{1/2}$	Half-Life
TLD	Total Lung Dose
ULN	Upper Limit of Normal
VA-ECMO	Veno-arterial Extracorporeal Membrane Oxygenation
VentaProst	VentaProst™ – Drug/device combination product consisting of aerosolized epoprostenol delivered via dedicated drug delivery system
VentaProst Nebulizer	The nebulizer assembly that is part of the VentaProst delivery system
VTE	Venous Thromboemobolism
VV ECMO	Venovenous Extracorporeal Membrane Oxygenation
WBC	White Blood Cell (count)
WHO	World Health Organization

2.1 Introduction

COVID-19 is a rapidly emerging pathogen that has recently been declared a pandemic by the World Health Organization (WHO). No targeted therapeutic treatments for coronavirus (COVID-19) have been identified. Symptoms range from mild upper respiratory tract infection to profound hypoxia, severe pneumonia, ARDS and death. Progression of end stage disease is unpredictable with high fatality rates in mechanically ventilated patients as a result of multi-organ failure. Among patients who require hospitalization, mortality may be 5% to 15%, and for those who become critically ill, reported mortality ranges from 22% to 62%.

Prostacyclin therapy—available in oral, inhaled, and intravenous forms—is an analogue which mimics endogenous prostacyclin (PGI2). Prostacyclin binds to its receptor (a G-protein coupled receptor) found on the surface of vascular smooth muscle and platelets, activates cyclic adenosine monophosphate (cAMP), and results in inhibition of platelet aggregation, vascular smooth muscle relaxation and vasodilation of the pulmonary arteries (Mitchell, Ali et al. 2008). Prostacyclins are most commonly used in the treatment of PAH due to their potent vasodilatory effects. In addition, prostacyclin analogs also inhibit platelet aggregation and may reduce prothrombotic effects of endothelin.

The rationale for use of vasodilators in COVID-19 patients rests on their rapid local effect on the pulmonary vasculature, which has shown to lead to increased oxygenation in other diseases, such as PAH (Higenbottam, Wheeldon et al. 1984) and post-surgical PH (De Wet, Affleck et al. 2004). Epoprostenol has the additional advantage over inhaled nitric oxide in that it may be directly administered through a standard ventilator (closed-circuit).

The rationale for aerosolized prostacyclin use in COVID-19 patients experiencing hypoxia leading to cardiac failure is two-fold:

(1) inhaled prostacyclin therapy has been used in the treatment of ARDS and has been shown to improve oxygenation and ventilation-perfusion mismatch (see Section 9). Prostacyclins, such as epoprostenol, promote pulmonary vasodilation via a cyclic adenosine monophosphate-mediated decrease in intracellular calcium (Figure 4). While it has not been associated with improved outcomes, such as mortality, and it's use in ARDS is off-label, it may be used in severe life-threatening hypoxemia refractory to conventional ARDS management, such as has been seen in COVID-19.

(2) The second potential benefit of prostacyclin therapy in the management of COVID-19 is to mitigate direct SARS-CoV-2-associated coagulopathy. Prostacyclins have anti-inflammatory (Dewachter 2012) and antiplatelet aggregation properties[1]. Microvascular thrombosis and large vessel venous thromboembolism have been described anecdotally and in case reports of corona virus infected patients and abnormal coagulation parameters are associated with increased mortality (Giannis, Ziogas et al. 2020). Inhibition of platelet aggregation occurs with prostacyclin therapy and may mitigate thrombosis in situ seen in PAH itself, and potentially in patients with COVID-19 associated respiratory illness.

Literature data with both inhaled NO and inhaled epoprostenol in ARDS, acute lung injury and severe hypoxemia show improvement of oxygenation (Afshari, Bastholm Bille et al. 2017), (Dzierba, Abel et al. 2014), decrease of pulmonary arterial pressure (Fuller, Mohr et al. 2015) and in some cases improvement in clinical outcomes such as shorter time on mechanical ventilation and shorter time in ICU (Ammar, Bauer et al. 2015). However, due to the heterogeneity of the population and the severity of the disease, not all studies agree on the effectiveness of inhaled epoprostenol, particularly to reduce mortality in ARDS (Adhikari, Dellinger et al. 2014), (Afshari, Bastholm Bille et al. 2017). Meta-analyses have concluded that the quality of the currently published data for the use of inhaled vasodilators in ARDS, ALI and refractory hypoxemia is insufficient to definitely conclude for or against their use (Afshari, Bastholm Bille et al. 2017), (Fuller, Mohr et al. 2015).

This study will evaluate the potential therapeutic benefit of VentaProst in treating patients with COVID-19 at risk for the progression of respiratory and/or cardiac/circulatory failure. This double-blind, placebo controlled study will assess the efficacy and safety of VentaProst at a range of 3.4-30.6 ng/kg/min for a maximum of 10 days at the discretion of the Investigator. The patient will be followed through Day 28 to assess their clinical status.

2.2 VentaProst

2.2.1 Nonclinical Experience

Refer to the current Investigator's Brochure (IB) for details of nonclinical pharmacology and toxicology studies with VentaProst.

2.2.2 Clinical Experience

There have been no clinical trials to date with VentaProst in COVID-19 patients (see Section 2.2.4 below for summary of clinical data with VentaProst in cardiac surgery patients).

2.2.3 Summary of Pharmacokinetic Results

Epoprostenol undergoes rapid chemical hydrolysis under physiological conditions to yield 6-keto-PGF1α and is also subject to enzymatic degradation. As such, it is only possible to evaluate the PK using radioactively labeled drug. Studies using 3H-epoprostenol sodium indicate half-life is generally less than 3 minutes with an I.V. bolus, and with I.V. infusion, plasma steady-state concentrations were achieved within 15 minutes of initiation of the infusions, and steady-state concentrations increased linearly with increasing infusion rate. Tissue distribution studies indicate the highest levels of radioactivity were observed in the kidney, liver, and small intestine and the lowest levels were observed in brain and adipose tissue. Epoprostenol-derived material is rapidly excreted into urine and feces after dosing with epoprostenol sodium.

There is only one study in the literature that reports the PK of inhaled epoprostenol. The study by Haraldsson (Haraldsson, Kieler-Jensen et al. 2000) was designed to evaluate the effects of inhaled epoprostenol on platelet aggregation after surgery. No differences were seen in 6-keto-PGF1α levels with two dose levels of epoprostenol compared to placebo

over six hours of administration in the ICU. Epoprostenol deposition in the lungs was not quantified, but the aerosol was administered only during the inspiratory phase of mechanical ventilation. The blood levels of 6-keto-PGF1α by enzyme immunoassay in this study were reported to be several times higher than other levels reported in the literature.

In 2017, Stanford University's Department of Cardiac Surgery conducted an observational study (IND129777, Report# APC-VP-CLN-004) investigating the levels of 6-keto-PGF1α in cardiac surgery patient requiring CPB. Sixteen patients were enrolled; eight did not received inhaled epoprostenol, eight received aerosolized epoprostenol at a nominal starting dose of 50 ng/kg/min.

Plasma levels determined in aerosol epoprostenol naïve patients indicates that cardiac surgery procedures, including CPB, result in elevated endogenous levels of both 6-keto-PGF1α and thromboxane B2. Delivery of aerosol epoprostenol in patients resulted in a further elevation of 6-keto-PGF1α levels, but not thromboxane B2.

While it proved difficult to delineate the endogenous and exogenous contributions of aerosol delivery during surgery, 6-keto-PGF1α levels declined rapidly in aerosol naïve patients during ICU stay. Examination of the 6-keto-PGF1α levels during weaning, after this endogenous decline, indicate that the overall aerosol delivery efficiency, nebulized to absorbed (deposited lung dose), is less than 8%. That is, out of a nominal dosing rate of 50 ng/kg/min only 4 ng/kg/min actually reaches the lungs and gets absorbed.
Comparison to recently published data (Nicolas, Krause et al. 2012) investigating 6-keto-PGF1α levels during steady state I.V. administration of Flolan indicates that the systemic exposure from aerosol delivery in cardiac surgery is similar to, or lower, than that experienced from intravenous administration of the approved Flolan product.

The findings of this observational PK study with inhaled epoprostenol are sufficient to make a correlation to historical systemic exposure levels with intravenous administered Flolan (the reference listed drug) and show levels of exposure similar to, or lower than, the currently approved intravenous product.

2.2.4 Summary of Clinical Results

The safety and tolerability of VentaProst were evaluated in a Phase 2a Clinical Study in cardiac surgery patients "*A Two-Part Pharmacodynamic Study to Compare VentaProst™ (Epoprostenol Solution for Inhalation via Custom Drug Delivery System) Dosing to Conventionally Administered Aerosolized Epoprostenol Dosing in Cardiac Surgery Patients*" (NCT03122730).

Overall, 15 patients were exposed to doses of VP from 3.4 to 20.4 ng/kg/min in this study. Administration of VP in this dose range was well-tolerated. Overall, there were 2 patients (28.6%) in Part I and 1 patient (12.5%) in Part II who experienced a total of 7 TEAEs. All 7 TEAEs were assessed by the investigator as related to the surgical procedure and as unrelated to the study drug and unrelated to the device. No deaths occurred during the study. A total of 3 patients had 1 SAE each. All 3 SAEs were considered to be unrelated to the study drug or the study device.

Seven patients were evaluated in Part I to determine the effective dose equivalence between VP delivered at 17 ng/kg/min and off-label aerosolized Veletri administered at 50 ng/kg/min during mechanical ventilation. In all patients, VP 17 ng/kg/min was found to be equivalent either by calculation of effect compared with aerosolized Veletri 50 ng/kg/min or the investigators' judgement. In most patients, no differences were observed in oxygen saturation ranges between VP and aerosolized Veletri treatments at the same FiO2 while on the ventilator. The investigator determined that oxygenation, assessed by oxygen saturation measurements, did not change disproportionately with ventilator operating parameters on VP compared with aerosolized Veletri.

Eight patients were evaluated in Part II of the study to identify the optimal dose of VP. In the investigator's judgement, the optimal VP dose was determined to be 6.8 ng/kg/min in 2 patients, 10.2 ng/kg/min in 3 patients, and 13.6 ng/kg/min in 3 patients, which is the minimal dose that reliably produced a maximum hemodynamic response in all patients.

There have been no clinical trials to date with VentaProst in COVID-19 patients.

See IB for additional clinical information regarding inhaled epoprostenol.

2.2.5 Summary of Known and Potential Risks of Inhaled Epoprostenol Administration

Safety of inhaled epoprostenol in cardiothoracic surgery patients is remarkable. In the reported literature to date, there were no reports of serious or life-threatening drug-related safety events. Due to its mechanism of action, inhaled epoprostenol may theoretically cause increased bleeding (anti-platelet mechanism) or systemic vasodilation consequent to spill over into the central circulatory system, but no such events have been reported. Some accounts of the use of inhaled prostacyclin in the chronic setting (e.g. iloprost for PAH) report transient events as listed on the approved product labeling. These include cough, headache, flushing, and an influenza-like syndrome. However, these types of events are unlikely to be reported due to sedation in the ICU setting.

VentaProst may result in hypotension, which will be monitored via frequent - assessments of oxygenation, ventilatory and hemodynamic parameters and vital signs. Pulmonary edema and pulmonary bleeding are potential risks due to the drug's mode of action (refer to Section 7.2.2). Worsening oxygenation is a theoretic concern through worsened ventilation/ perfusion matching. This will be monitored through continuous pulse oximetry throughout the administration of the inhaled epoprostenol.

Risks to subjects in this study are related to common procedures performed (e.g., venipuncture) and the documented adverse events (AEs) listed in the current Investigator's Brochure. These risks are communicated to the subjects in the consent forms. There may be additional risks that are currently unknown.

The benefits of the study may include targeted lung vasodilation and improved oxygenation, potential anti-platelet effects on the lung vasculature, reduction in disease progression, avoidance of greater oxygen needs and early weaning off mechanical ventilation. If the drug does have such properties, then this may aid recovery, improve

outcomes and enable an earlier discharge from the hospital.
There is no funding awarded to the patients participating in this study.

2.2.6 Dosing Rationale for VentaProst

Literature on the current use of aerosolized epoprostenol in cardiac surgery and in ARDS shows a wide range and technically variable dosing for lowering PVR (Rao, Ghadimi et al. 2018), (Kallet, Burns et al. 2017), (Fuller, Mohr et al. 2015). Most of the experience is with continuous nebulization by commercially available nebulizers in various positions in mechanical ventilator circuits at doses of 50 ng/kg/min. Unlike the commercially available nebulizer systems, the VentaProst delivery platform aerosolizes epoprostenol only during the inspiratory cycle of the ventilator and administers respirable sized aerosol droplets (3-5 μm) in close proximity to the ETT of mechanically ventilated patients.

The assumed effect of the current continuous dosing regimen of 50 ng/kg/min is that the hemodynamic response is maximized and that no further improvements would be seen by increasing the dose. The initial in vitro estimate of the equivalent VentaProst (VP) dose to a 50 ng/kg/min conventional dose of continuously aerosolized Veletri was 17 ng/kg/min, which was the starting dose in Part I of the APC-VP-CLN-001 Phase 2a study conducted by Aerogen Pharma. During Part I of the study, it was determined that this dose is equivalent to 50 ng/kg/min epoprostenol delivered off-label via a generic nebulizer and continuous delivery. In Part II of the APC-VP-CLN-001 Phase 2a study, the VP dose escalation started from an initial dose of 3.4 ng/kg/min (20% of the equivalent dose). The dose was then increased in 3.4 ng/kg/min increments. Part II of the study was designed to demonstrate that the dose-response plateau could be achieved using lower VP doses than the initial estimated equivalent dose in Part I. Doses up to 30.6 ng/kg/min were approved for use in the study. In Part I of the study one patient, per the investigator discretion, received a 20.4 ng/kg/min dose. In Part II of the study it was determined that the optimal VP dose of 6.8 ng/kg/min in 2 patients, 10.2 ng/kg/min in 3 patients, and 13.6 ng/kg/min in 3 patients provided stable hemodynamic response. Based on these data, the recommended starting dose of VP, will be 13.6 ng/kg/min, as this dose is anticipated to produce the maximum hemodynamic response.

The proposed nominal dosing regimen for this COVID-19 trial is for up to 10 days of breath-synchronized aerosol delivery with a starting dose of study drug 13.6 ng/kg/min. Based on hemodynamic and oxygenation parameters, the dose can be titrated in 3.4 ng/kg/min steps up to a maximum of 30.6 ng/kg/min or down to a minimum of 3.4 ng/kg/min while patients are on mechanical ventilation. Of this nominal dosing rate approximately 30% will reach and deposit in the lung. Thus, the maximum Lung Dosing Rate (LDR) is ~10 ng/kg/min and the maximum Total Lung Dose (TLD) is ~ 144 μg/kg (Refer to VP IB Edition 6 dated 17-Jun-2020).

The inhalation toxicology program for VentaProst, originally designed for the cardiac surgery indication, covered a maximum LDR of 320 ng/kg/min and 60 ng/kg/min and a maximum TLD of 1091.4 μg/kg and 172.8 μg/kg in rats and dogs respectively. The LDR and TLD margins over the proposed maximum clinical exposure are thus 32 and 6, and 7.6 and 1.2, in rats and dogs respectively.

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is the reduction of respiratory, cardiac or circulatory failure in patients with confirmed COVID-19.

3.2 Secondary Objectives

The secondary objective in this study is to evaluate the effects of VentaProst on improvement in oxygenation, improvement in clinical outcomes and safety and tolerability.

The study will also evaluate the effects of VentaProst on inflammatory parameters in subjects with confirmed COVID-19.

3.3 Study Design

This is a double-blind, placebo controlled study of VentaProst (Active) as compared to placebo (Control). Active is inhaled epoprostenol administered via the VentaProst delivery system in 10 COVID-19 positive patients. Control is inhaled 0.9% sodium chloride solution administered via the VentaProst delivery system in 10 COVID-19 positive patients. Throughout the remainder of the protocol both Active and Control will be referred to as "study drug". This study will evaluate the potential therapeutic benefit of VentaProst in treating patients with COVID-19 who require mechanical ventilation and are at risk for the progression of respiratory and/ or cardiac/circulatory failure. This study will assess the efficacy and safety of VentaProst at an initial dose of 13.6 ng/kg/min (A range from 3.4-30.6 ng/kg/min may be administered as clinically required for a maximum of 10 days at the discretion of the Investigator. Patients will be followed through Day 28 to assess clinical outcomes.

Patients will be consented and randomized to either the Active or Control group within 48 hours of being placed on mechanical ventilation. Patients will be administered study drug using the VentaProst delivery system which allows up and down titration of study drug to achieve hemodynamic and oxygenation stability. The starting dose of study drug will be initiated at 13.6 ng/kg/min. Based on hemodynamic and oxygenation parameters, the dose of study drug can be increased in 3.4 ng/kg/min increments up to a maximum of 30.6 ng/kg/min or down to a minimum of 3.4 ng/kg/min.

All study staff with the exception of the unblinded pharmacist and Sponsor CRA will be blinded to which treatment regimen a patient has been assigned. Titration and weaning will be performed the same for all patients. Study drug will be administered based on the pump rate calculated for active treatment in mL/hr. Titration guidelines are provided in Section 5.3.3 and Table 3.

3.4 Duration of Participation

Patients who meet entry criteria will be entered into the study and the duration of study participation for each patient is listed below. The duration of study participation for each patient is as follows:

- Screening: up to 14 days
- Treatment: up to 10 days
- Follow up: 28 days

4. SELECTION AND WITHDRAWAL OF PATIENTS

Approximately 20 COVID-19 positive patients requiring mechanical ventilation will be enrolled in this study. Ten study participants will be randomized to either Active (inhaled epoprostenol administered via the VentaProst delivery system) treatment or Control (inhaled 0.9% sodium chloride solution administered by the VentaProst delivery system at calculated rates (mL/hr) used for the aerosolized epoprostenol). Study drug will indicate both Active and Control treatments.

Patients who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to enroll into the study.

4.1 Inclusion Criteria

Patients are eligible for this study if they meet all of the following criteria:

1. Women and Men Age ≥18 years old (no upper limit)
2. Confirmed COVID-19 positive by RT-PCR test
3. Patients who require invasive mechanical ventilation.
4. Enrolled into study within 48 hours of being placed on mechanical ventilation
5. Consent or professional consent obtained
6. Duration of shortness of breath must be within the previous 14 days.
7. Female subjects of childbearing potential must have a negative pre-treatment pregnancy test (serum or urine).
8. Received or currently receiving dexamethasone therapy for COVID-19
9. Willing and able to comply with treatment schedule and follow-up.

4.2 Exclusion Criteria

Patients are **NOT** eligible for this study if they meet any of the following criteria:

1. Patients on ECMO support.
2. Patients receiving another inhalation research medication or inhaled nitric oxide.
3. Not expected to survive for 48 hours.
4. Pregnant (positive pregnancy test in a pre-dose examination) or breastfeeding
5. Open tracheostomy.
6. Clinical contra-indication, as deemed by the attending physician.
7. Allergy to Epoprostenol and its diluent
8. Using inhaled vasodilators at baseline.
9. Patients who are hemodynamically unstable as determined by investigator
10. Patients with significant hemoptysis as determined by investigator

4.3 Re-Screening of Patients

Patients may not be enrolled more than once.

4.4 Removal of Patients from Therapy or Assessment

Aerogen Pharma or the Investigator may discontinue patients from the study at any time for safety or administrative reasons.

The End of Treatment Study procedures (Day 10) are to be completed for all patients who discontinue from the study (except Screen Failure patients).

The Investigator will promptly explain to the patient or their LAR that the study will be discontinued for the patient and provide appropriate medical treatment and other necessary measures for the patient.

Patients who discontinue early from the study will be discontinued for one of these primary reasons: Adverse events, patient death, lost to follow-up, patient withdrew consent, protocol violation, lack of efficacy, investigator decision, study terminated by sponsor, screen failure, or other. Study disposition information will be collected on the Patient Disposition DCF.

4.4.1 Criteria for Stopping VentaProst Treatment

Individual patients stopping criteria: At any time during study drug administration , patients may be removed from study treatment and placed on standard of care (SoC) therapy if they meet one or more of the following pre-defined criteria leading to a deterioration in their condition:

- Severe hypotension as evidenced by a systolic BP < 90 mmHg or MAP < 60 mmHG for >2 hours from the start of VentaProst
- Need for VV ECMO
- Need to increase existing vasopressor therapy by more than 25%
- Worsening oxygenation, ventilatory, or hemodynamic parameters that in the opinion of the investigator the patient should be removed from study treatment
- Massive hemoptysis thought to be clinically significant and not due to endotracheal tube trauma
- Pulmonary Edema
- If a clinically inadequate response is observed

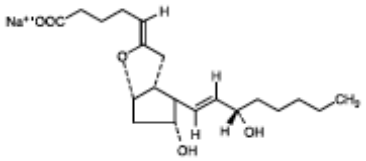
Study stopping criteria: If 3 patients are removed from the study for any of the above conditions, the study will stop further enrollment and investigation will be conducted to determine the cause of the events. An independent safety evaluation will also be conducted. If it is suspected that the investigational product has caused the events, the study will be terminated.

Independent Safety Evaluation: Independent safety evaluation will be conducted by a licensed physician who is not involved in the VentaProst COVID-19 clinical study or the sponsoring organization.

5. STUDY TREATMENTS

5.1 Identity of Medication Component of the Investigational Product

The study medication VentaProst, Flolan (epoprostenol sodium), is manufactured by GlaxoSmithKline and has been analyzed and released according to their specifications. The labelling of Flolan and placebo for this clinical trial will follow the protocols and procedures set forth by OSU's Investigational Drug Services (IDS). The Control for this study is 0.9% sodium chloride solution, USP from the OSU IDS stock and will be labeled in a blinded manner per the IDS protocols for maintenance of study blind.

Drug Substance Name	Epoprostenol Sodium
Chemical Name	5Z,9α,11α,13*E*,15*S*)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-1-oic acid.
Molecular Formula	$C_{20}H_{31}NaO_5$
Structural Formula	
Molecular Weight	374.45

5.1.1 Storage Condition

Both the vials of study medication and sterile diluent buffer should be stored between 20º to 25ºC (68º to 77ºF) with excursions permitted to 15° to 30°C (59° to 86°F) and kept in the supplied carton to protect the product from light. Study medication will be stored in a secure, controlled-access location at the study sites.

The 0.9% sodium chloride solution will be stored according the the product labelling.

5.2 Treatments Administered

Patients will receive study drug via mechanical ventilator, starting at 13.6 ng/kg/min. If determined by the treating physician, study drug can be up titrated in 3.4 ng/kg/min increments to a maximum of 30.6 ng/kg/min or down to a minimum of 3.4 ng/kg/min. At the Investigator's discretion, the patient will be weaned off the drug in 3.4 ng/kg/min increments. Study drug will be administered based on the pump rate calculated for the active treatment but delivered in mL/hr. Study drug can be administered up to 10 days.

5.3 Study Medication Supply, Preparation, and Administration

5.3.1 Study Medication Supply

The medicinal component of VentaProst, Flolan, (epoprostenol sodium), is already approved for I.V. delivery. The dosage form is a vial of 1.5 mg epoprostenol as a

lyophilizate and the required pH 12 Sterile Flolan diluent per the currently approved packet insert (NDA20-444/ Supplement 24[1]). Flolan and its diluent (pH 12 Sterile Diluent) are not re-formulated by Aerogen Pharma. Flolan is used with the same diluent system and reconstituted per the approved packet insert.

Flolan and diluent container closure (glass vial and stopper/crimp-pH 12 Sterile Diluent for Flolan comes in a plastic bottle for mixing) and secondary packaging (cardboard box) are not being altered, including the information on the vial and box label and the information in the approved Flolan packet insert. This preserves the approved drug labeling information per NDA 20-444.

Placebo will be a corresponding volume of 0.9% sodium chloride solution from the OSU IDS stock.

5.3.2 Study Medication Preparation

Refer to the VentaProst-COVID Pharmacy Manual for preparation of study drug solution..

Prior to use, drug solutions must be protected from light and refrigerated at 2° to 8°C (36° to 46°F) if not used immediately. Do not freeze drug solutions and discard any drug solution that has been frozen. Discard any drug solutions if refrigerated for more than 8 days. Control, (0.9% sodium chloride solution) will be placed in identical syringes and masked according OSU IDS procedures for blinded studies.

5.3.3 Study Medication Administration

In the ICU, patients will be started on study drug administered via the VentaProst delivery system at an initial dose administered at 13.6 ng/kg/min. Study Drug Study drug may be titrated up or down in 3.4 ng/kg/min increments (refer to VentaProst Pharmacy Manual) as clinically indicated to a dose range of 3.4-30.6 ng/kg/min. Study drug will be administered based on the pump rate calculated for the active treatment in mL/hr. Study drug can be administered up to 10 days.

[1] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020444s024lbl.pdf

Table 3: Administration Titration Guidelines

Up titration Guideline	Downward Titration / Guideline
Start Dose: 13.6 ng/kg/min 1st Step Up Dose (17.0) 2nd Step Up Dose (20.4) 3rd Step Up Dose (23.8) 4th Step Up Dose (27.2) 5th Step Up Dose (30.6)	Start Dose: 13.6 ng/kg/min 1st Step Down dose (10.2) 2nd Step Down Dose (6.8) 3rd Step Down dose (3.4)

All study drug will be administered per the calculated pump rate for the active treatment in ml/hr

Table 4-Example of Up Titration for male with Ideal Body Weight of 70 kg

Initial Dose Rate	Initial Pump Rate	New Dose Rate	New Pump Rate
13.6 ng/kg/min	1.89 mL/hr	13.6 ng/kg/min	1.89 mL/hr
		17.0 ng/kg/min	2.39 mL/hr
		20.4 ng/kg/min	2.86 mL/hr
		23.8 ng/kg/min	3.33 mL/hr
		27.2 ng/kg/min	3.81 mL/hr
		30.6 ng/kg/min	4.28 mL/hr

Active drug is prepared with 50 mL in each syringe at a concentration of 30,000 ng/mL.
All study drug will be administered per the calculated pump rate for the active treatment in ml/hr.

5.3.4 Study Medication Weaning

Patients will be weaned from study drug slowly to avoid rebound vasoconstriction. During weaning, doses will be decreased in steps of 3.4 ng/kg/min increments, with a minimum of 15 minutes between changes. The weaning process should occur in isolation to other treatment changes (no changes in inotropes, vasopressors, or vasodilators) whenever possible. Patients will be observed closely before, during, and after dose changes. In the event patients demonstrate signs of hemodynamic instability or a decrease in oxygenation indicated by pulse oximetry during downward titration, the dose will be returned to its previous level. Once patients have been stable for at least 15 minutes, repeat attempts at dose reduction may be undertaken. The process will continue until patients are fully weaned. Patients will be monitored for safety and efficacy throughout study drug administration.

5.4 Identity of the Device Component of the Investigational Product

5.4.1 Identity of Device

The Phase 2a VentaProst drug delivery system is designed to accurately and precisely administer aerosol to the lungs of critically ill patients who require support via mechanical ventilation. The aerosol generator's fundamental operating mechanism and materials of construction will be similar to the 510(k)-cleared Aeroneb Solo System (K120939, K103635, K070642, Aerogen Ltd) and it is being designed for compatibility with the range of ventilators found in the OR and ICU.

5.4.1.1 VentaProst Aerosol Delivery to Ventilated Patients

The VentaProst delivery system (Figure 1) consists of reusable and single-patient use disposable elements:

1. Reusable multi-patient use components consist of two electronic controllers with power supplies, Aerogen Solo Nebulizer Cable, and Sensirion Flow Sensor Cable. When used together, they synchronize aerosol generation with the patient's inspiratory pattern through a single-patient use, disposable administration kit.
    - Aerogen Pro-X, is a commercially available device (K120939[2]) cleared for use to continuously operate the disposable Aerogen Solo nebulizer. (item #1 Figure 1).
    - Aerogen Pharma Controller (AP Controller) is an investigational device, which synchronizes aerosol generation with the ventilator inspiratory cycle (item #2 on Figure 1). This controller was tested to demonstrate its safety for use under IND129777.
    - Aerogen Solo Nebulizer Cable
    - Sensirion Flow Sensor Cable
2. Single-patient disposable kit:
    - Aerogen Solo nebulizer (item #3 on Figure 1) is a commercially available, low mass and low profile vibrating mesh aerosol generator (K070642) cleared for use with the Aerogen Pro-X controller and Aerogen Continuous Nebulization Tube Set (CNTS).
    - Aerogen CNTS and syringe (items #4 and 5 on Figure 1) is a commercially available device (K103635) cleared for use to connect to the Aerogen Solo and deliver medication from the drug reservoir (syringe) to the mesh the nebulizer.
    - Flow sensor and cable connected to the Aerogen Pharma Controller (AP Controller, item #7 on Figure 1). This is a new component of the system, which was tested to demonstrate safety for use in a clinical study.

The VentaProst delivery system will be used in conjunction with a commercially available and FDA-cleared syringe pump (item #8 on Figure 1). In general, any available syringe pump, which (1) is compatible with the Aerogen Continuous Nebulization Tube Set (CNTS syringe and tubing), and (2) is capable of delivering medication to the vibrating mesh nebulizer within the range of 0.4 to 12.0 mL/h as required to deliver the doses specified in the APC-VPCOV-CLN-001 Pharmacy Manual. For purposes of the VPCOV study, Aerogen Pharma will supply the Perfusor® Space Infusion Syringe Pump System from B.Braun (Figure 1). This particular syringe pump is FDA-cleared (K093913), it is compatible with the CNTS syringe (items #4 on Figure 1) and is able to

[2] The product names for the Aerogen commercial products changed from the term "***Aeroneb***", to the brand name "***Aerogen***". A Note to File was submitted to FDA and receipt was acknowledged by the Branch Office

deliver fluids in the rage of 0.4 to 12.0 mL/h. It is worth noting that on 11 April 2020, this pump received EUA for use in the tracheal delivery of continuous nebulized medications into a nebulizer to treat patients of all ages with or suspected of having the Coronavirus Disease 2019 (COVID-19)[3].

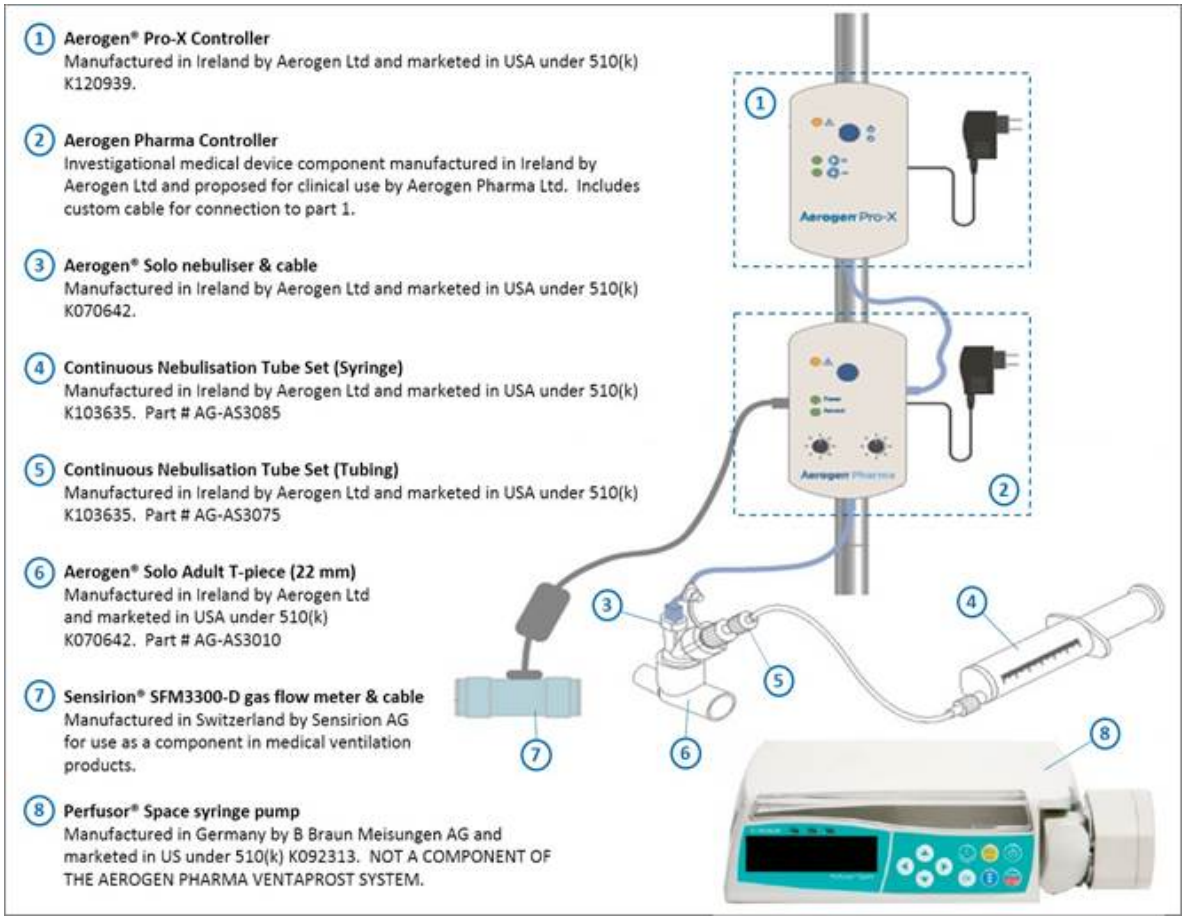


Figure 1: Drug Delivery System

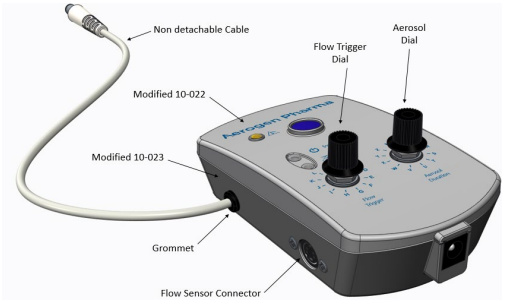
The Aerogen Pro-X (item #1, Figure 1), Aerogen Solo (item #3, Figure 1) are mounted on an I.V. pole at the patient's bedside. The two controllers and Aerogen CNTS (items #4 and 5, Figure 1) are routinely used as a system within their intended use. The sensor and nebulizer are connected into specific locations of the inspiratory limb of the ventilator pre- and post the humidifier, respectively (see Figure 2). The addition of the AP Controller and an off-the shelf Sensirion flow sensor enables the VentaProst system to synchronize aerosol delivery with the inspiratory cycle of the ventilator (Figures 1 and 2).

Figure 2 illustrates the AP Controller, which is similar to the commercially available

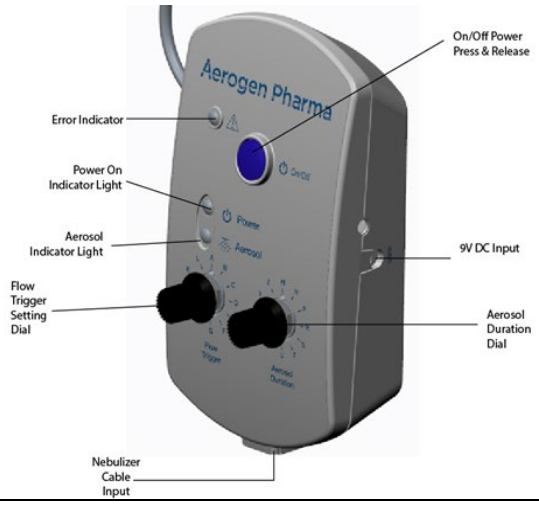
[3] https://www.fda.gov/media/136894/download

Aerogen Pro-X controller in form, size, weight and materials used for the upper and lower shells. The AP Controller uses the same AC/DC adapter and cable as used in the commercial Aerogen Pro-X controller. The packaging used for the AP Controller is same as packaging validated by Aerogen Ltd. for the commercially available Aerogen Pro-X system. Functionality of the AP Controller was tested in design verification studies (IND129777). Two dials (Figure 2) are used to: (1) set the flow threshold for nebulization triggering during the inspiratory cycle of the ventilator, accommodating initial ventilator baseline bias flows, and (2) set the duration of nebulization during the inspiratory cycle (a detailed description of the mechanism of action of the AP Controller is presented in IND129777).

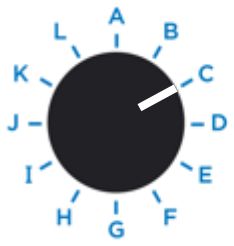
A. Diagram of Aerogen Pharma Controller (left side view)



B. Diagram of Aerogen Pharma Controller (right side view)



C. Flow Trigger Dial settings



A	2.5slm
B	4.0slm
C	5.5slm
D	7.0slm
E	8.5slm
F	10.0slm
G	11.5slm
H	13.0slm
I	14.5slm
J	16.0slm
K	17.5slm
L	19.0slm

D. Aerosol Duration Dial settings

M	0.3sec
N	0.4sec
P	0.5sec
R	0.6sec
S	0.7sec
T	0.8sec
U	0.9sec
V	1.0sec
W	1.1sec
X	1.2sec
Y	1.3sec
Z	1.4sec

Figure 2: Aerogen Pharma Controllers

Prior to administration, study drug will be prepared per the VP COVID Pharmacy Manual and placed into a 60 mL CNTS syringe. The syringe will be labeled to maintain the study blind. The user will attach the syringe to the CNTS tubing and prime the tube set so that the formulation reaches the Aerogen Solo, producing aerosol generation. The CNTS syringe set will be placed in a B Braun Perfusor Space Infusion syringe pump. The 15-mm T-Piece with nebulizer is placed between the ventilator circuit and the ETT (Figure 2). The user will select the pump rate (mL/hr) to deliver the recommended dose based on

the ideal body weight in kilograms (kg) dispensed to achieve the dose rate in ng/kg/min for active treatment. The control treatment's corresponding pump flow rate in mL/hour will be calculated based on initial dose of Flolan in ng/kg/min. All study drug will be administered per the calculated pump rate for active treatment in ml/hr. The user will be able to adjust this recommended dose up or down (per protocol) by changing pump rate prior to selecting dose and initiating delivery. The selected dose will then be dispensed by the pump to the receiving surface of the mesh, resulting in generation of an aerosol with a volume median diameter in the range of 2 to 5 µm. The Aerogen Pharma Controller monitors the patient's breathing pattern and user adjusts the knob (on left) to initiate aerosol generation at the beginning of the breathing cycle. The knob on right sets the duration of aerosol generation within each breath.

The VentaProst device is designed to be compatible with standard intensive care unit (ICU) equipment. The following site-specific equipment will be needed to deliver the therapy: B.Braun syringe pump (provided by Aerogen Pharma), ventilator, endotracheal tube (ETT), humidifier, ventilator circuit. This equipment is standard for critical care medicine.

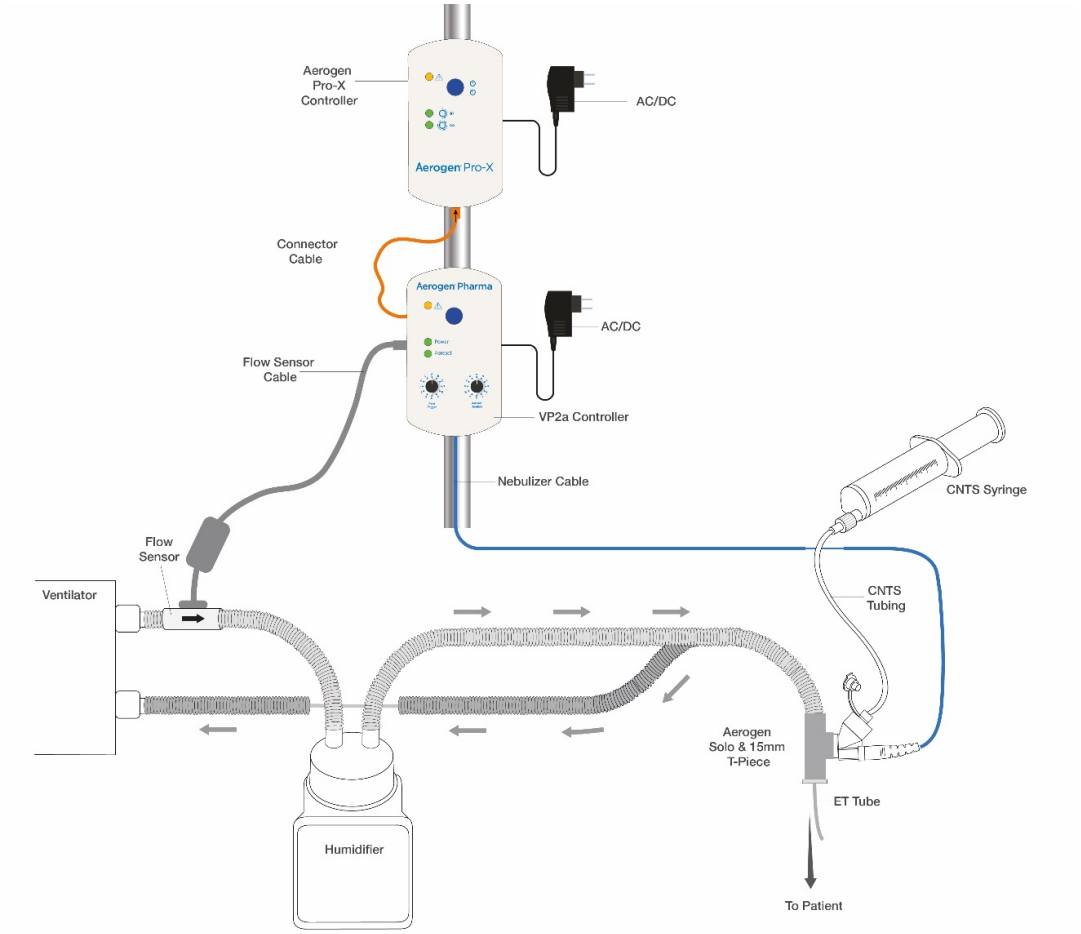


Figure 3 - VentaProst Device Placement in the Gas Pathway

5.4.2 Ventilator Settings

The device is designed for use with standard adult ventilator settings. An intermittent positive pressure ventilatory mode (i.e., not constant positive airway pressure [CPAP] or t-piece) is required to activate the device to deliver aerosol during the inspiration phase. A Heat-Moisture Exchanger (HME) may be used in the device circuit.

The site will utilize OSU's Standard of Care (SOC) mechanical ventilation guidelines for care of patients for COVID-19 with ARDS. The following ventilator parameters will be assessed daily while on VentaProst: Ventilator type, Mode, FiO_2, Inspiratory Time, Mean Airway Pressure, Peak Inspiratory Pressure, Positive End Expiratory Pressure, Respiratory Rate and Tidal Volume.

5.4.3 Device Supply

All device supplies will be provided by Aerogen Pharma Limited (including the B.Braun Syringe Pump). The serial numbers for the controllers, flow sensor, and nebulizer will also be recorded in an IP accountability dispensing log.

Used and unused devices will be inventoried and returned to the Sponsor or Sponsor's designee.

5.4.4 Device Replacement

Devices may be replaced at any time if there a suspicion of malfunction, but must be replaced if:

- The investigator suspects that, due to device malfunction, less than 90% of the total dose of study drug has been delivered. Reduced doses must be estimated and recorded in the patient's medical record and source documentation.
- The investigator suspects the device is not performing optimally for any reason.

5.4.5 Device Malfunction or Failure

One device (Aerogen Pro-X controller, Aerogen Pharma Breath Controller, Flow Sensor, Solo nebulizer, CNTS tubing and syringe, and associated components) is expected to perform throughout the duration of study treatment. If the controllers, Flow Sensor, CNTS tubing and syringe, or the Solo nebulizer are not functioning optimally for any reason, instructions for trouble-shooting provided in the device instruction for use manual should be followed. If one or more devices need to be replaced, the reason should be documented in the patient's medical record, dispensing log, and Device Performance Issues Form. Additional devices are provided for this purpose. The unique serial numbers of the new components will be recorded in the patient's medical record, dispensing log, and the source documentation.

For device malfunction or complaints, complete the Device Performance Issues Log and submit to the Sponsor at Complaints@aerogenpharma.com within 48 hours. Failed devices will be set aside from the general supplies, inventoried and returned to the Sponsor or the Sponsor's designee.

5.5 Blinding

Clinical and research staff and Sponsor will be blinded to Active or Control dose assignments with the exception of the pharmacy staff and an unblinded Sponsor CRA. Should unblinding be necessary, the medical monitor for this study will work with the unblinded pharmacist or unblinded CRA to unblind the patient.

Active treatment (Flolan) is clear in color when reconstituted and Control treatment (0.9% sodium chloride solution) is also clear in color to maintain the study blind. The Control and Active treatments will be placed in identical 60 mL syringes and labelled in a blinded manner prior to leaving the pharmacy.

5.6 Prior and Concomitant Therapy

For patients who receive study drug, any medication (including over-the-counter [OTC] medications or other investigational therapies) or therapy administered to the patient during the course of the study (starting at Screening and 14 days prior) will be recorded on the Prior and Concomitant Therapy data collection forms. The Investigator will record any AE on the AE data collection forms for which a concomitant medication/therapy was administered.

5.6.1 Prohibited Concomitant Therapy

Other inhaled vasodilators.

5.7 Investigational Product (IP) Supplies and Accountability

Investigational product supplies will not be sent to the Investigator(s) until the following documentation has been received by the Sponsor:

- Written proof of approval of the protocol and its informed consent forms (ICFs) by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for the institution where the study is to be conducted. (Due to COVID-19 and the availability of the Active study medication, the study medication will be sent to the OSU pharmacy and held in quarantine until IRB approval and the completion of Study Initiation Visit (SIV), which may be conducted remotely or in person. A NTF will be sent to OSU pharmacy instructing that the study medication not be released for use until Sponsor notification.)
- An Investigator-signed and dated FDA Form 1572.
- A signed and dated curriculum vitae of the Principal Investigator including a copy of the Principal Investigator's current medical license (required in the US) or medical registration number on curriculum vitae.

The Investigator and study staff will be responsible for the accountability of all IP supplies (dispensing, inventory, and record keeping) following Aerogen Pharma instructions and adhere to Good Clinical Practice (GCP) guidelines as well as local and/or regional requirements.

Under no circumstances will the Investigator allow the IP to be used other than as directed by this protocol. IP will not be administered to any individual who is not enrolled into the study.

An accurate and timely record of the receipt of all IP; dispensing of IP to the patient; collection of unused IP; and subsequent return of unused IP to Aerogen Pharma must be maintained. This includes, but may not be limited to: (a) documentation of receipt of IP, (b) IP dispensing log, (c) IP accountability log, (d) all shipping service receipts, and (e) documentation of returned IP to the Sponsor. All forms will be provided by Aerogen Pharma. Any comparable forms that the investigational site wishes to use must be approved by Aerogen Pharma.

The supplies and inventory records must be made available, upon request, for inspection by the designated representative of Aerogen Pharma, a representative of the FDA, or a representative of a non-US health authority. All used and unused IP are to be returned to Aerogen Pharma at the conclusion of the study.

6. CRITERIA FOR EVALUATION

6.1 Primary Endpoint

1. Reduction of respiratory failure. Failure is defined by any one of the following:

    - Requires VV ECMO
    - Inability to extubate within 10 days or reintubation within < 24 hours
    - Change in S/F, oxygenation index and P/F ratio ($\geq$15%) from baseline to 12 hours, Days 1, 2, 3, 4, 5, 6, 7, 8, 9 and Day 10 (or end of treatment)

or

1. Reduction of cardiac or circulatory failure. Failure is defined by any one of the following:

    - Need to begin inotropic therapy or 10% increase in current vasopressor therapy
    - Worsening hemodynamic parameters
    - Cardiac troponin >20% from baseline
    - BNP $\geq$ 15% of baseline
    - Need for temporary mechanical circulatory support (IABP, Impella)
    - Requires VA ECMO

6.2 Secondary Endpoints

1. Improvement in oxygenation defined as any one of the following:
    - Stabilization of PaO2/FIO2 >250
    - Improvement in FIO2 by 50% or improvements $\geq$15% in S/F, P/F ratio from baseline at 12 hours, Day 5 and Day 10 (or end of treatment)
2. Improved clinical outcomes defined as one of more of the following:
    - Time to extubation following the site's extubation protocol

- Free from re-intubation
- Reduction in ICU days
- Reduction in the number of re-admissions to the ICU due to COVID-19 within 28 days
- Reduction in total hospital days
- Mortality [28 days] defined as Cardiopulmonary mortality or mortality from all causes

3. Safety and tolerability
    - Monitoring of adverse events (AEs), serious adverse events (SAEs), chest CT or Chest X-rays, vital signs, ventilatory/oxygenation parameters, and laboratory tests.

6.3 Exploratory endpoints will include (where available):

- Change in LDH
- Change in fibrinogen
- Change in WBC count including lymphocytes and neutrophil subsets
- Change in triglycerides
- Change in ferritin
- Change in CRP / ESR
- Change in IL-6
- Change in D-Dimer

Changes in these parameters will be assessed for each patient from baseline to end of study as well as changes between the active and control groups.

6.4 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used and generally recognized as reliable, accurate, and relevant in studies of cardiac and respiratory function.

7. SAFETY ASSESSMENTS

Safety will be assessed through monitoring of adverse events (AEs) and serious adverse events (SAEs), laboratory tests, chest assessments (Chest CT or Chest X-ray), oxygenation/ventilatory parameters, and vital signs. Safety assessment frequency is shown in the Schedule of Assessments and Procedures.

7.1 General Safety Procedures

7.1.1 Vital Signs and Weight Measurements

Vital sign measurements, including systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) [beats per minute], respiratory rate (breaths per minute), and body temperature (in Celsius) will be obtained twice daily Days 1-10 or as clinically indicated. Weight (kg) will be obtained at the time of Screening and at Day 10 or end of VP treatment. Height will be obtained at the time of Screening. If unable to obtain height, the study staff will use the best reported historical height from patient or LAR.

7.1.2 Physical Examination

A physical examination will be conducted at the screening visit and will include assessments of general appearance; skin and lymphatics; eyes, ears, nose, throat; cardiovascular system; respiratory system; abdomen/gastrointestinal system; urological system; musculoskeletal and neurological systems. Other body systems may be examined as clinically indicated.

7.1.3 Laboratory Measurements

Clinical laboratory measurements to be performed are listed below. The Schedule of Assessments and Procedures shows the time points at which blood will be collected for clinical laboratory tests and pregnancy testing. The Baseline for laboratory tests is the Screening assessment.	
Category	Parameters
Hematology-CBC with diff	Hemoglobin, hematocrit, RBC, WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelets
Full Chemistry Panel	
Electrolytes	Sodium, potassium, chloride, bicarbonate, calcium
Liver function tests	AST, ALT, AP, total bilirubin
Renal function parameters	BUN, creatinine
Coagulation Studies	PT/PTT
Other	Serum or urine pregnancy test, RT-PCR for COVID-19, ESR, Troponin, BNP, fibrinogen, ferritin, LDH, Triglycerides, D-Dimer, IL-6, and CRP

7.1.4 Chest Assessments

A Chest CT or Chest X-ray will be obtained at Screening and Day 5.

7.1.5 Time Prone Protocol

The time prone protocol is a standard of care in OSU's ICU. This will be in place for all days that patients are within the ICU.

7.2 Adverse Events

7.2.1 Definitions

Adverse events are any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. For the purposes of this study, this will include unanticipated medical events in the judgment of the investigator. ***A pre-existing condition*** or symptom

is one that is present at the start of the study and is reported as part of the patient's medical history. A pre-existing condition or symptom should be reported as an AE only if its frequency, intensity or character worsens during study treatment.

All AEs that occur from the time of the first dose of study medication through the End of Study (Day 28) will be recorded and reported as Treatment-Emergent Adverse Events (TEAE). All AEs must be appropriately documented in the patient's medical chart/source documentation and on the DCFs. When known, investigators should report syndromes rather than list symptoms associated with the syndrome.

All AEs that are ongoing at the conclusion of the study should be followed until: a) resolution/stable sequelae; b) the Investigator determines that it is no longer clinically significant; or, c) the study patient is lost to follow-up. If no follow-up is provided, the Investigator must provide a written justification.

7.2.2 Adverse Events of Special Interest (AESI)

Pulmonary edema and pulmonary hemorrhage are AEs of special interest due to the mode of action of epoprostenol. If an AE of special interest occurs, the Sponsor will be notified of this occurrence within 24 hours.

7.2.3 Grading of Adverse Events

The severity of each AE will be categorized using the following criteria:

- Grade 1 (Mild): usually transient; requires no special treatment and does not interfere with the patient's daily activities.
- Grade 2 (Moderate): produces a low level of inconvenience to the patient and may interfere with daily activities. These AEs are usually ameliorated by simple therapeutic measures.
- Grade 3 (Severe): interrupts daily activity and requires systemic drug therapy or other medical treatment.

7.2.4 Relationship to Study Medication/Study Device/Procedure

The Investigator must assess the relationship of each reported AE. The Investigator must make an assessment of the relationship of the AE to the study drug/study device/procedure using the following scale:

- Unrelated: The AE is definitely not or unlikely to be associated with study medication/study device/procedure and is judged due to causes other than the study medication/study device/procedure.
- Related: The AE is possibly or probably related with study medication/study device/procedure.

7.2.5 AE Outcomes

The following terms and definitions are used in assessing the final outcome of an AE:

- Recovered/Resolved - The patient has fully recovered, or by medical or surgical treatment, the condition has returned to the level observed at the first trial-related

activity.

- Recovering/Resolving - The condition is improving and the patient is expected to recover from the event.
- Recovered/Resolved with sequelae - The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- Not recovered/Not resolved - The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known at the time of reporting.
- Fatal - This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as "recovered", "recovering", "recovered with sequelae" or "not recovered". An AE with fatal outcome must be reported as an SAE.

7.2.6 Laboratory Test and other Test Abnormalities as Adverse Events

A laboratory or other test (chest assessments, vital signs) abnormality should be reported as an AE if the Investigator considers the abnormality an AE or if the abnormality is associated with accompanying symptoms, requires medical/surgical intervention, leads to a change in study treatment, or results in discontinuation from the trial. When possible, syndromes not laboratory values, should be reported as AEs. For example, elevated hepatic transaminases associated with hepatitis should be reported as "hepatitis" and decreased hemoglobin and hematocrit requiring iron supplementation should be recorded as "anemia." Prior to reporting as an AE, abnormal tests should be repeated to verify the accuracy of the original result.

7.2.7 Serious Adverse Events

The Investigator is required to determine if each AE is a Serious Adverse Event (SAE). An SAE is any AE occurring after randomization and through Day 28 and results in any of the following outcomes:

- Death, or
- Is life-threatening, or
- Prolongation of existing hospitalization, or
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- Is a congenital anomaly/birth defect.

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

In the event of death, the cause of death should be recorded as the SAE (death is an outcome, not the AE itself).

Any planned procedures that require admission to hospital as well as any planned elective procedures (e.g., angioplasty) are not considered SAEs (unless the underlying condition has worsened or the procedure results in a worsening of the patient's condition). In addition, pregnancy that occurs during the course of the study or absence of a treatment effect will also not be considered to be an SAE and will be collected on a separate CRF.

7.2.8 Reporting for SAEs (24 Hours)

Regardless of causality, an SAE must be followed clinically until resolution or stabilization.

All SAEs after randomization and through Day 28 of the study must be reported to the Sponsor or the Sponsor's representative within 24 hours of the investigational site's knowledge of the occurrence. The investigational site will email a Serious Adverse Event Report (SAER) to the Sponsor and the Medical Monitor. Investigational sites will be provided with SAER forms. The Medical Monitor will work closely with the Sponsor to properly assess and report the SAE.

The SAE information emailed to the Sponsor or the Sponsor's representative will include the following (as available):

- Patient Number, Investigator name, and Site Number
- SAE information: event term, onset date, severity, and causal relationship
- Basic demographic information (e.g., age, gender, weight)
- The outcomes attributable to the event (death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, other important medical event[s])
- A summary of relevant test results, pertinent laboratory data, and any other relevant medical history
- The first and last dates of study drug administration.
- A statement whether study medication was discontinued or study medication administration schedule modified
- A statement whether event recurred after reintroduction of study medication if administration had been discontinued or withheld
- Supplemental anonymized information may include the following hospital records: laboratory results, radiology reports, progress notes, admission and emergency room notes, holding/observation notes, discharge summaries, autopsy reports, and death certificates

Supplemental information may be transmitted using a follow-up report and should not delay the initial report.

For regulatory purposes, initial reports of SAEs should be transmitted within the prescribed time frame as long as the following minimum information is available: patient number, suspect study medication, reporting source, and an event or outcome that can be

identified as being both serious and unexpected for which the Investigator can make a relationship assessment.

7.3 Reporting of Pregnancy

Any pregnancy where the estimated date of conception occurs either prior to the End of Study must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment. The medical monitor may decide that unblinding of the patient treatment assignment may be necessary.

An induced abortion or a spontaneous abortion is considered to be an SAE and should be reported in the same timeframe and in the same format as all other SAEs.

Pregnancies must be reported as soon as possible but no later than one business day by email.

All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but not later than 24 hours of the investigational site's knowledge of the outcome.

8. PHARMACOKINETIC ASSESSMENTS

Not applicable.

9. SCHEDULE OF ASSESSMENTS AND PROCEDURES

The assessments and procedures for this study are described in detail below and presented in the Schedule of Assessments and Procedures located behind the Synopsis.

9.1 Study Evaluation Timepoints

9.1.1 Screening (within 14 days prior to Baseline Day 1)

Potential study patients will be recruited by the study staff from patients. The following assessments will occur prior to study enrollment:

- Informed consent prior to any study procedures or assessments being performed.
- Demographic Information
- Medical History
- Physical Exam
- Prior Medication History
- Chest CT or Chest X-ray
- Inclusion/Exclusion Eligibility Assessment (including assessment of shortness of breath within the last 14 days)

- Serum/Urine Pregnancy Test (if woman of childbearing potential)
- Clinical Laboratory Sampling to include: Full Chemistry Panel including LFTs, CBC with Diff including neutrophils and lymphocytes, PT/PTT, Triglycerides, LDH, ferritin, fibrinogen, CRP, ESR, IL-6, troponin, BNP, D-Dimer, and RT-PCR for COVID-19
- Vital Signs
- Height & Weight (If height can't be obtained, use the best reported historical height)

9.1.2 Days 1-10 Treatment

9.1.2.1 Randomization

- Evaluate that the patient continues to be eligibile for the study by assessing Inclusion/Exclusion Criteria.
- Once eligibility has been confirmed, a Subject number beginning with 101 and rising sequentially will be assigned to the next enrolled subject.
- A blinded order for the Investigational Drug Services group will be generated by EPIC for the next sequential subject to be randomized.
- The unblinded pharmacist will prepare the treatment assignment (Active or Control) for the next assigned Subject number.
- The reconstituted study drug will be protected from light and labelled in a blinded manner to ensure maintenance of the study blind.
- Subjects will be randomized to receive either Active or Control for a maximum of 10 days, as clinically indicated and at the discretion of the Investigator.

9.1.2.2 Baseline-Day 1 (0 Hour)

- Continue evaluation eligibility by assessing Inclusion/Exclusion Criteria.
- Study drug treatment will begin at a starting dose of 13.6 ng/kg/min based on the concentration used to calculate Active treatment in mL/hr and can be titrated up to 30.6 ng/kg/min or down to 3.4 ng/kg/min as clinically warranted. The B.Braun syringe pump will be set to the appropriate dose in mL/hr utilizing the subject's sex and height (ideal body weight).
- Vital signs will be assessed twice daily in AM and PM while on study drug. Efforts will be made to obtain vital signs at the same time each day. Vital signs include: temperature, pulse rate, respiration rate and blood pressure.
- Adverse Event/SAE assessment daily
- Concomitant medication evaluation daily
- Continuous pulse oximetry (SpO_2)
- Ventilatory parameters assessed twice daily while on study drug: Ventilator Type, Vent Mode, FiO_2, Inspiratory time, Mean Airway Pressure, Peak Inspiratory Pressure, Positive End Expiratory Pressure, Tidal Volume, and Respiratory Rate
- Time Prone Position-16 hours per day per OSU Protocol

9.1.2.3 Day 1-12 hours

- Clinical Laboratory Sampling to include: Full Chemistry Panel including LFTs, CBC with Diff including neutrophils and lymphocytes, PT/PTT, Triglycerides, LDH, ferritin, fibrinogen, CRP, ESR, IL-6, troponin, BNP, and D-Dimer.
- Continue to administer study drug if clinically indicated.
- Adverse Event/SAE assessment daily
- Concomitant medication evaluation daily
- Oxygenation measurement via continuous pulse oximetry (SpO_2)
- Ventilatory parameters assessed twice daily while on study drug: Ventilator Type, Vent Mode, FiO_2, Inspiratory time, Mean Airway Pressure, Peak Inspiratory Pressure, Positive End Expiratory Pressure, Tidal Volume, and Respiratory Rate
- Vital signs will be assessed twice daily in AM and PM. Efforts will be made to obtain vital signs at the same time each day. Vital signs include: temperature, pulse rate, and blood pressure.
- Time Prone Position-16 hours per day per OSU Protocol

9.1.2.4 Days 2-10 (While on study drug)

- Continue to administer study drug if clinically indicated.
- Adverse Event/SAE assessment daily
- Concomitant medication evaluation daily
- Oxygenation measurement via continuous pulse oximetry (SpO_2)
- Ventilatory parameters assessed twice daily: Ventilator Type, Vent Mode, FiO_2, Inspiratory time, Mean Airway Pressure, Peak Inspiratory Pressure, Positive End Expiratory Pressure, Tidal Volume, and Respiratory Rate
- Vital signs will be assessed twice daily in AM and PM. Efforts will be made to obtain vital signs at the same time each day. Vital signs include: temperature, pulse rate, and blood pressure.
- Time Prone Position-16 hours per day per OSU Protocol
- Full Chemistry Panel including LFTs, CBC with Diff including neutrophils and lymphocytes, PT/PTT and RT-PCR for COVID-19. (Day 5 only)
- Chest CT or Chest X-ray (Day 5 only)

- Full Chemistry Panel including LFTs, CBC with Diff including neutrophils and lymphocytes, PT/PTT, Triglycerides, LDH, ferritin, fibrinogen, CRP, ESR, IL-6, troponin, BNP, D-Dimer, and RT-PCR for COVID-19 (Day 10 only).

- Obtain weight. (Day 10 only or at end of study drug dosing)

9.1.2.5 Weaning

See Section 5.3.4 and Table 3 for weaning guidelines.

9.1.3 Day 28/End of Study (EOS)

- Assess AEs/SAEs
- Assess Mortality
- Assess concomitant medications

9.2 Data Collection

Investigator or designee will enter the information required by the protocol onto source documents and enter data into data collection forms (DCFs) in an excel spreadsheet provided by Aerogen Pharma.

9.3 Clinical Data Management

Data from source documents will be verified against the DCF and any discrepancies will be clarified and resolved with study staff.

9.4 Database Quality Assurance

All data will be remotely monitored by the Sponsor due to the COVID-19 pandemic. Should restrictions be lifted at OSU, an on-site visit may occur if all parties are in agreement.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Methods

A Statistical Analysis Plan will be not be developed as this is an exploratory trial. Any statistical evaluation will be handled internally by Aerogen Pharma or their designee.

10.2 Determination of Sample Size

The number of patients has been selected to enable an adequate clinical assessment of pharmacodynamics, safety, and tolerability parameters without presenting undue risk to a large number of patient's being exposed to this investigational product.

10.3 Analyses Sets

All patients who are enrolled in the study and who receive at least one dose of study drug will be included in the intent-to-treat (ITT) analyses of pharmacodynamic and safety data. All available data will be used and missing data will not be estimated or carried forward

in any statistical summary or analyses.

Descriptive summary statistics include the number of patients, mean, median, percent coefficient of variation (% CV) (if required), standard deviation, and minimum and maximum values (quantitative variables) or the number of patients and percentages by category (qualitative variables). Changes will be assessed as the difference between baseline measurements and the appropriate post-dose measurements unless otherwise specified. Mean differences between active and control groups (when available) will be assessed and significance will be determined on the basis of a 95% CI. Individual patient listings of data will also be provided to allow for review of all pharmacodynamic, safety, and tolerability parameters.

10.4 Randomization

Patients will be randomized 1:1. A randomization schedule will be provided to the unblinded pharmacist. Should unblinding be requested due to a medical emergency, the unblinded pharmacist will work with the medical monitor or Sponsor unblinded CRA to obtain the required information.

10.5 Demographic and Other Baseline Characteristics

Continuous demographic and other baseline characteristics (such as age, weight, and height) will be summarized using n, mean, SD, median, minimum, and maximum. Qualitative characteristics (such as gender and race) will be summarized by counts and percentages.

10.6 Criteria for Evaluation

10.6.1 Primary Efficacy Endpoint

The primary efficacy endpoint:

1. Reduction of respiratory failure. Failure is defined by any one of the following:

    - Requires VV ECMO
    - Inability to extubate patient within 10 days or reintubation within <24 hours
    - Change in S/F, oxygenation index and P/F ratio (≥15%) from baseline to 12 hours, Days 1, 2, 3, 4, 5, 6, 7, 8, 9 and Day 10 (or end of treatment)

or

2. Reduction of cardiac or circulatory failure. Failure is defined by any one of the following:

    - Need to begin inotropic therapy or 10% increase in current vasopressor therapy
    - Worsening hemodynamic parameters
    - Cardiac troponin >20 % from baseline
    - BNP ≥ 15% of baseline

- Need for temporary mechanical circulatory support (IABP, Impella)
- Requires VA ECMO

10.6.2 Secondary Efficacy Endpoints

Key secondary endpoints include:

1. Improvement in oxygenation defined as any one of the following:
   - Stabilization of PaO2/FIO2 >250
   - Improvement in FIO2 by 50% or improvements ≥15% in S/F, P/F ratio from baseline at 12 hours, Day 5 and Day 10 (or end of treatment)
2. Improved clinical outcomes defined as one of more of the following:
   - Time to extubation following the site's extubation protocol
   - Free from reintubation
   - Reduction in ICU days
   - Reduction in the number of re-admissions to the ICU due to COVID-19 within 28 days
   - Reduction in total hospital days
   - Mortality [28 days] defined as Cardiopulmonary mortality or mortality from all causes
3. Safety
   - Monitoring of adverse events (AEs), serious adverse events (SAEs), chest CT or Chest X-rays, vital signs, ventilatory/oxygenation parameters, and laboratory tests.

10.6.3 Key Exploratory Endpoints include:

- Change in LDH
- Change in fibrinogen
- Change in WBC count including lymphocytes and neutrophil subsets
- Change in triglycerides
- Change in ferritin
- Change in CRP / ESR
- Change in IL-6
- Change in D-Dimer

Changes in these parameters will be assessed for each patient from baseline to end of study as well as changes between the active and control groups.

10.7 Extent of Exposure

Exposure data will be summarized by using frequencies and percentages.

10.8 Safety Analyses

Safety measurements include AE/SAEs, vital signs, chest assessments (Chest CT or Chest X-ray), laboratory tests, and oxygenation/ventilatory parameters. Safety data will be summarized by using frequencies and incidence rates.

10.8.1 Adverse Events

AEs will be classified into standardized medical terminology from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be presented by preferred term nested within System Organ Class. Verbatim description and all MedDRA level terms, including the lower level terms, for all AEs will be contained in the data listings of the clinical study report (CSR).

AEs will be summarized by presenting the incidence of AEs. Although a MedDRA term may be reported more than once for a patient, that patient will be counted only one time in the incidence count for that MedDRA term.

Treatment-emergent adverse events (TEAEs) will be analyzed. AEs that are not treatment-emergent will be listed. A TEAE is defined as

- AEs that emerge during treatment, having been absent at pretreatment, or
- Reemerge during treatment, having been present at pretreatment but stopped prior to treatment, or
- Worsen in severity or frequency during treatment relative to the pretreatment state, when the AE is continuous.

Adverse events of special interest (AESI) will be analyzed. An AESI is defined as:

- Serious or non-serious adverse that is one of scientific and medical concern specific to the sponsor's product for which ongoing monitoring and rapid communication by the investigator to the sponsor is required
- Events or symptoms thought to potentially be associated with the investigational compound, device, or disease under study, or
- Can arise with any use of a drug/device (e.g. off-label use, use in combination with another approved drug), with any route of administration, formulation, or dose, including an overdose.

10.8.2 Laboratory Values

Clinical laboratory results post-Baseline will be evaluated for markedly abnormal values. For the incidence of markedly abnormal laboratory values, each patient may be counted once in the laboratory parameter value high and in the laboratory parameter low categories as applicable. Descriptive summary statistics (e.g. mean, SD, median, minimum, maximum) for laboratory values and changes from baseline will be evaluated.

10.8.3 Vital Signs

Vital sign values will be evaluated on an individual basis by patient. Abnormal vital sign values will be identified as those outside (above or below) the reference range. Descriptive summary statistics (e.g., mean, SD, median, minimum, maximum) for vital sign parameters and changes from Baseline will be evaluated.

10.9 The Procedure for Revising the Statistical Analysis Plan

Not Applicable.

11. ADMINISTRATIVE PROCEDURES AND INSTRUCTIONS

11.1 Ethics

11.1.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an IRB or IEC constituted and functioning in accordance with International Conference on Harmonization (ICH) E6, Section 3, and any local regulations, i.e., Federal Regulations, Title 21 Code of Federal Regulations (CFR) Part 56. Any protocol amendment and/or revision to the ICF will be resubmitted to the IRB/IEC for review and approval (except for changes involving only logistical or administrative aspects of the study (e.g., change in CRA[s], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

A signed letter of study approval from the IRB/IEC Chairman must be sent to the Principal Investigator with a copy to the Sponsor prior to study start. If the IRB/IEC decides to suspend or terminate the study, the Investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the Sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the Investigator or Sponsor, depending on local regulatory obligations. If the Investigator is required to report to the IRB/IEC, he/she will forward a copy to the Sponsor at the time of each periodic report. The Investigator or the Sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable AEs per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the Investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

11.1.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating practices of Aerogen Pharma (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- ICH - E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonization of Pharmaceuticals for Human Use.

- US CFR dealing with clinical studies (21 CFR, including parts 50 and 56 concerning Informed Patient Consent and IRB regulations).

11.1.3 Patient Information and Informed Consent

As part of administering the informed consent document, the Investigator must explain to each patient or their legally authorized representative (LAR), the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, and currently available alternative treatments. Each patient must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The patient or their LAR should understand the statement before signing and dating it and will be given a copy of the signed document. The patient or their LAR will be asked to sign an informed consent prior to any study-specific procedures being performed. No patient can enter the study before his/her informed consent has been obtained. Due to the COVID-19 pandemic and restrictions on hospital visitors, informed consent may be obtained via telephone or video conference call if the patient is incapacitated or sedated due to the severity of their illness. A witness for the study team should be present when a call or video conference is occurring with the patient's LAR. This process should be carefully documented in the subject's medical records.

An unsigned copy of an IRB/IEC and Sponsor-approved written informed consent must be prepared in accordance with ICH E 6, Section 4, and all applicable local regulations, i.e., Federal Regulations, Title 21, CFR Part 50, and provided to the Sponsor. Each patient or their LAR must sign (or give verbal consent with study staff witnessing the verbal consent) an approved informed consent prior to study participation. The form must be signed and dated by the appropriate parties. The original signed ICF for each patient will be verified by the Sponsor and kept in the study center's investigational site files.

The patient should be informed in a timely manner if new information becomes available that might be relevant to the patient's willingness to continue participation in the trial. The communication of this information should be documented.

11.2 Administrative Procedures

11.2.1 Changes to the Protocol

There are to be no changes to the protocol without written approval from the Sponsor. Protocols will be followed as written.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of patients, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRBs/IECs of all investigational sites and, as required, by the regulatory authority. These requirements

should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all patients included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary for safety reasons, the Medical Monitor must be notified promptly and the IRB/IEC for the site must be informed as soon as possible.

Changes affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval, but the IRB/IEC must be kept informed of such changes. In these cases, the Sponsor will send a letter to the site for forwarding on to the IRB/IEC detailing such changes.

11.2.2 Adherence to the Protocol

The Investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.2.3 Monitoring Procedures

The Sponsor or Sponsor's representative will maintain contact with the Investigator and designated staff by telephone, letter, and/or email between study visits. Monitoring visits to each investigational site will be conducted by the sponsor either remotely or in person.

In accordance with ICH E6, Section 6.10, source documents include, but are not limited to the following:

- Clinic, office, hospital charts.
- Copies or transcribed health care provider notes which have been certified for accuracy after production.
- Recorded data from automated instruments such as mechanical ventilators, x-rays, and other imaging reports, e.g., sonograms, computed tomography scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, electroencephalographs, polysomnography, pulmonary function tests (regardless of how these images are stored, including microfiche and photographic negatives).
- Records of telephone contacts.
- Diaries or evaluation checklists.
- Investigational product distribution and accountability logs maintained in pharmacies or by research personnel.
- Laboratory results and other laboratory test outputs, e.g., serum pregnancy test result documentation.
- Correspondence regarding a study patient's treatment between physicians or memoranda sent to the IRBs/IECs.
- CRF components (e.g., questionnaires) that are completed directly by patients and serve as their own source.

11.2.4 Recording of Data

In order to provide the Sponsor with accurate, complete, and legible records following criteria are to be maintained. The Investigator will enter the information required by the protocol onto the data collection forms (DCFs) provided by the sponsor as agreed upon with the research staff.

11.2.5 Data Storage and Retention of Records

The circumstances of completion or termination of the study notwithstanding, the Investigator has the responsibility to retain all study documents, including but not limited to the protocol, copies of data collection forms (DCFs) , Investigator's Brochure, regulatory agency registration documents, e.g., FDA 1572 form, ICFs, and IRB/IEC correspondence. The investigational site should plan on retaining study documents as follows:

- For at least two years following the date a marketing application is approved for the investigational product for the indication for which it is being investigated, or
- Until two years after the investigation is formally discontinued and no application is to be filed or if the application is not approved.

It is requested that at the completion of the required retention period, or should the Investigator retire or relocate, the Investigator contacts the Sponsor, allowing the Sponsor the option of permanently retaining the study records.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Data will be coded (de-identified), stored in a secure electronic database during and after the study, and will not be shared with unauthorized persons. The principal investigator and co-investigator will have access to the data to review and analyze the data, as described in this protocol. For the protection and privacy of the patients, no identifying information will be released. Data will be retained and possibly used in the future for further analysis. All identifiers will be removed and not be shared at any time.

11.2.6 Handling of Investigational Product

Investigational study drug (Flolan) will be inventoried and maintained within the site's Investigational Drug Services . It will be stored according to their protocols and procedures. The study drug should not be dispensed to patients in the VentaProst COVID trial (APC-VPCOV-CLN-001) until a favorable IRB approval has been obtained by the OSU IRB and a study initiation visit has been conducted by the Sponsor. Investigational device supplies must be kept in an appropriate secure area (e.g., locked cabinet) and stored according to the conditions specified on the investigational product labels. The Investigator (or designated pharmacist) must maintain an accurate record of the shipment and dispensing of the IP (both device and drug) in an IP accountability log, a copy of which must be given to the Sponsor at the end of the study. An accurate record of the date and amount of IP dispensed to each patient must be available for inspection at any time. The assigned sponsor representative will review these documents along with all other study conduct documents at an appropriate interval of visit to the investigational

site once IP has been received by the investigational site. Due to COVID-19 a physical inventory of IP (drug and device supplies) may not be possible. If at all possible, an inventory of supplies should be conducted via video conferencing. If video conferencing is not possible, study staff will inventory supplies and provide documentation to Aerogen Pharma.

All IP supplies (with the exception of OSU stock 0.9% sodium chloride solution supplies) are to be used only for this protocol and not for any other purpose. The Investigator (or designated pharmacist) must not destroy any IP product labels or any partly used or unused IP supply without Sponsor authorization. At the conclusion of the study and as appropriate during the course of the study, the Investigator (or designated pharmacist) will return or properly dispose of all used IP. Unused investigational device and drug components will be returned to Aerogen Pharma at the conclusion of the study.

11.2.7 Publication of Results

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each Investigator and Aerogen Pharma, as appropriate.

11.2.8 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the course of this study will be kept confidential by the Investigator, the Investigator's staff, and IRB/IEC and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study without the written consent of the Sponsor. No data collected as part of this study will be utilized in any written work, including publications, without the written consent of Sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in the Confidentiality Agreement between the Sponsor and the Investigator. All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Confidentiality Agreement between the Investigator and Sponsor (provided by the Sponsor).

11.2.9 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time.

The Investigator reserves the right to discontinue the study should his/her judgment so dictate. If the Investigator terminates or suspends a trial without prior agreement of the Sponsor, the Investigator should inform the Institution where applicable, and the Investigator/Institution should promptly inform the Sponsor and the IRB/IEC and should provide the Sponsor and the IRB/IEC a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.2.10 Patient Insurance and Indemnity

The Sponsor will provide the insurance in accordance with local guidelines and requirements as a minimum for the patients participating in this study.

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PROTOCOL TITLE	**TITLE: DOUBLE-BLIND, PLACEBO CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF VENTAPROST (INHALED EPOPROSTENOL DELIVERED VIA DEDICATED DELIVERY SYSTEM) IN SUBJECTS WITH COVID-19 REQUIRING MECHANICAL VENTILATION**
PROTOCOL NUMBER	APC-VPCOV-CLN-001
INVESTIGATIONAL PRODUCT	VentaProst™
INDICATION	Reduction of respiratory, cardiac or circulatory failure in patients with COVID-19
PHASE	Phase 2a
SPONSOR	Aerogen Pharma Limited 1660 S Amphlett Boulevard, Suite 360 San Mateo, CA 94402 United States
MEDICAL MONITOR	Matthew Exline, MD
AMENDMENT #3 APPROVAL DATE	14 December 2020
GCP STATEMENT	This study is to be performed in full compliance with International Conference on Harmonization (ICH) and all applicable local Good Clinical Practices (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
CONFIDENTIALITY STATEMENT	This document is confidential as it contains proprietary information of Aerogen Pharma. Any viewing or disclosure of such information that is not authorized in writing by the Aerogen Pharma is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

SPONSOR PROTOCOL APPROVAL PAGE

PROTOCOL TITLE	**A DOUBLE-BLIND, PLACEBO CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF VENTAPROST (INHALED EPOPROSTENOL DELIVERED VIA DEDICATED DELIVERY SYSTEM) IN SUBJECTS WITH COVID-19 REQUIRING MECHANICAL VENTILATION**
PROTOCOL NUMBER	**APC-VPCOV-CLN-001**
AMENDMENT #3 APPROVAL DATE	**14 December 2020**

Judy Doto, RN, BSN Date
Head of Clinical Operations
Aerogen Pharma

Jim Fink PhD, RRT, FCCP Date
Chief Scientific Officer
Aerogen Pharma

Plamena Entcheva-Dimitrov, PhD, RAC Date
Head of Regulatory and Medical Affairs
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Andy Clark PhD Date
Vice President and General Manager
Aerogen Pharma

INVESTIGATOR'S SIGNATURE PAGE

PROTOCOL TITLE	**A DOUBLE-BLIND, PLACEBO CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF VENTAPROST (INHALED EPOPROSTENOL DELIVERED VIA DEDICATED DELIVERY SYSTEM) IN SUBJECTS WITH COVID-19 REQUIRING MECHANICAL VENTILATION**
PROTOCOL NUMBER	**APC-VPCOV-CLN-001**
AMENDMENT #3 APPROVAL DATE	**14 December2020**

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with ICH-GCPs and all applicable local guidelines.

_____

Principal Investigator (printed/typed)

_____

Principal Investigator Signature Date

1. CLINICAL PROTOCOL SYNOPSIS

Sponsor	Aerogen Pharma
Protocol No.	APC-VPCOV-CLN-001
Title of Study	Double-blind, placebo controlled study to assess the efficacy and safety of VentaProst (Inhaled epoprostenol delivered via dedicated delivery system) in subjects with COVID-19 requiring mechanical ventilation.
Study Centers	One clinical site in the US
Phase	Phase 2a
Objectives	**Primary Objective:** The primary objective of this study is the reduction of respiratory, cardiac or circulatory failure in patients with confirmed COVID-19. **Secondary Objectives:** The secondary objective in this study is to evaluate the effects of VentaProst on improvement in oxygenation and improvement in clinical outcomes. The study will also evaluate the effects of VentaProst on inflammatory parameters in subjects with confirmed COVID-19.
Study Design	This is a double-blind, placebo controlled study of VentaProst (Active) as compared to placebo (Control). Active is inhaled epoprostenol administered via the VentaProst delivery system in 10 COVID-19 positive patients. Control is inhaled 0.9% sodium chloride solution administered via the VentaProst delivery system in 10 COVID-19 positive patients. Throughout the remainder of the protocol both Active and Control will be referred to as "study drug". This study will evaluate the potential therapeutic benefit of VentaProst in treating patients with COVID-19 who require mechanical ventilation and are at risk for the progression of respiratory and/ or cardiac/circulatory failure. This study will assess the efficacy and safety of VentaProst at an initial dose of 13.6 ng/kg/min (A range from 3.4-30.6 ng/kg/min may be administered as clinically required for a maximum of 10 days at the discretion of the Investigator. Patients will be followed through Day 28 to assess clinical outcomes. Patients will be consented and randomized to either the Active or Control group within 48 hours of being placed on a mechanical ventilator. Patients will be administered study drug using the VentaProst delivery system which allows up and down titration of study drug to achieve hemodynamic and oxygenation stability. The starting dose of study drug will be initiated at 13.6 ng/kg/min. Based on hemodynamic and oxygenation parameters, the dose of study drug can be increased in 3.4 ng/kg/min increments up to a maximum of 30.6 ng/kg/min or down to a minimum of 3.4 ng/kg/min. Study drug will be administered based on the pump rate calculated for active treatment in mL/hr. The titration table below (Table 1) shows the typical up and down titration steps for study drug.

	Table 1: Overview of Titration and Weaning Guidelines **Up titration Guideline*** / **Downward Titration / Weaning Guideline**** Start Dose: 13.6 ng/kg/min / Start Dose: 30.6 ng/kg/min 1st Step Up Dose (17.0) / 1st Step Down dose (23.8) 2nd Step Up Dose (20.4) / 2nd Step Down Dose (17.0) 3rd Step Up Dose (23.8) / 3rd Step Down dose (10.2) 4th Step Up Dose (27.2) / 4th Step Down dose (3.4) 5th Step Up Dose (30.6) * The study drug will be administered based on the pump rate calculated for active treatment in mL/hr.**If the patient has been up-titrated weaning should occur from that level in 6.8 ng/kg/min decrements. Patients will be weaned from study drug slowly to avoid rebound vasoconstriction. During weaning, doses will be decreased in steps of 6.8 ng/kg/min increments, with a no less than 5 minutes between changes as clinically appropriate. The weaning process should occur in isolation to other treatment changes (no changes in inotropes, vasopressors, or vasodilators) whenever possible. Patients will be observed closely before, during, and after dose changes. In the event patients demonstrate signs of hemodynamic instability or a decrease in oxygenation indicated by pulse oximetry during downward titration, the dose will be returned to its previous level. Once patients have been stable for at least 15 minutes, repeat attempts at dose reduction may be undertaken. The process will continue until patients are fully weaned. Patients will be monitored for safety and efficacy throughout study drug administration.
Number/Type of Patients	Approximately 20 COVID-19 positive patients requiring mechanical ventilation will be enrolled in this study. Patients will be randomized to either VentaProst Active (aerosolized epoprostenol administered via the VentaProst delivery system) or VentaProst Control (aerosolized 0.9% sodium chloride solution administered via the VentaProst delivery system).
Inclusion Criteria	Patients are eligible for this study if they meet all of the following criteria: 1. Women and Men Age ≥18 years old (no upper limit) 2. Confirmed COVID-19 positive by a diagnostic test such as molecular or antigen test 3. Patients who require invasive mechanical ventilation. 4. Enrolled into study within 48 hours of being placed on mechanical ventilation 5. Consent or professional consent obtained 6. Duration of shortness of breath must be within the previous 14 days. 7. Female subjects of childbearing potential must have a negative pre-treatment pregnancy test (serum or urine). 8. Received or currently receiving dexamethasone for the treatment of COVID.

	9. Willing and able to comply with treatment schedule and follow-up.
Exclusion Criteria	Patients are **NOT** eligible for this study if they meet any of the following criteria: 1. Patients on ECMO support. 2. Patients receiving another inhalation research medication or inhaled nitric oxide. 3. Not expected to survive for 48 hours. 4. Pregnant (positive pregnancy test in a pre-dose examination) or breastfeeding 5. Open tracheostomy. 6. Clinical contra-indication, as deemed by the attending physician. 7. Allergy to Epoprostenol and its diluent 8. Using inhaled vasodilators at baseline. 9. Patients who are hemodynamically unstable as determined by investigator 10. Patients with significant hemoptysis as determined by investigator
Study Treatment(s)	Patients will receive study drug via mechanical ventilator, starting at 13.6 ng/kg/min. If determined by the treating physician, study drug can be up titrated in 3.4 ng/kg/min increments to a maximum of 30.6 ng/kg/min or down to a minimum of 3.4 ng/kg/min. At the Investigator's discretion, the patient will be weaned off the drug in 6.8 ng/kg/min increments. Study drug will be administered based on the pump rate calculated for active treatment in mL/hr. Study drug can be administered up to 10 days.
Duration of Treatment	The duration of study participation for each patient is as follows: • Screening: up to 14 days • Treatment: up to 10 days • Follow up: 28 days
Criteria for Evaluation	<u>Primary Endpoint</u> 1. Reduction of respiratory failure. Failure is defined by any one of the following: • Requires VV ECMO • Inability to extubate patient within 10 days or reintubation within < 24 hours • Change in S/F, oxygenation index and P/F ratio (≥15%) from baseline to 12 hours, Days 1, 2, 3, 4, 5, 6, 7, 8, 9 and Day 10 (or end of treatment) **or** 2. Reduction of cardiac or circulatory failure. Failure is defined by any one of the following: • Need to begin inotropic therapy or 10% increase in current vasopressor therapy • Worsening hemodynamic parameters • Cardiac troponin > 20% from baseline • BNP ≥ 15% of baseline • Need for temporary mechanical circulatory support (IABP, Impella) • Requires VA ECMO <u>Secondary Endpoints:</u> 1. Improvement in oxygenation defined as any one of the following: • Stabilization of PaO2/FIO2 >250 • Improvement in FIO2 by 50% or improvements ≥15% in S/F, P/F ratio from baseline at 12 hours, Day 5 and Day 10 (or end of treatment)

	2. Improved clinical outcomes defined as one of more of the following: • Shorter time to extubation following the site's extubation protocol • Free from reintubation • Reduction in ICU days • Reduction in the number of re-admissions to the ICU due to COVID-19 within 28 days. • Reduction in hospital days Mortality (28 Days) defined as Cardiopulmonary mortality or mortality from all causes. 3. Safety and tolerability: • Monitoring of adverse events (AEs), serious adverse events (SAEs), chest CT or Chest X-rays, vital signs, ventilatory and oxygenation parameters, and laboratory tests. **Exploratory endpoints will include (where available as part of standard of care):** 1. Change in LDH 2. Change in fibrinogen 3. Change in WBC count including lymphocytes and neutrophil subsets 4. Change in triglycerides 5. Change in ferritin 6. Change in CRP / ESR 7. Change in IL-6 8. Change in D-Dimer Changes in these parameters will be assessed for each patient from baseline to end of study as well as changes between the active and control groups.
Ventilatory Parameters	OSU SOC: Ventilator Type (GE) Parameters to monitor are: 1. Ventilator Mode 2. FiO_2 3. Inspiratory Time 4. Mean Airway Pressure 5. Peak Inspiratory Pressure 6. Positive End Expiratory Pressure 7. Respiratory Rate 8. Tidal Volume
Criteria for Stopping VentaProst Treatment	**Individual patients stopping criteria:** At any time during study drug administration, patients may be removed from study treatment and placed on standard of care (SoC) therapy if they meet one or more of the following pre-defined criteria leading to a deterioration in their condition: • Severe hypotension as evidenced by a systolic BP < 90 mmHg or MAP < 60 mmHG for >2 hours from the start of VentaProst • Need for VV ECMO • Need to increase existing vasopressor therapy by more than 25%

	• Worsening in oxygenation, ventilatory, or hemodynamic parameters that in the opinion of the investigator the patient should be removed from study treatment • Massive hemoptysis thought to be clinically significant and not related to endotracheal tube trauma • Pulmonary edema **Study stopping criteria:** If 3 patients are removed from the study for any of the above conditions, the study will stop further enrollment and an investigation will be conducted to determine the cause of the events. An independent safety evaluation will also be conducted. If it is suspected that the investigational product has caused the events, the study will be terminated. **Independent Safety Evaluation:** Independent safety evaluation will be conducted by a licensed physician who is not involved in the VentaProst COVID-19 clinical study or the sponsoring organization.
Statistical Methods	All patients who are enrolled in the study and who receive at least one dose of study drug will be included in the intent-to-treat (ITT) analyses of pharmacodynamic and safety data. All available data will be used and missing data will not be estimated or carried forward in any statistical summary or analyses. Descriptive summary statistics include the number of patients, mean, median, percent coefficient of variation (% CV) (if required), standard deviation, and minimum and maximum values (quantitative variables) or the number of patients and percentages by category (qualitative variables). Changes will be assessed as the difference between baseline measurements and the appropriate post-dose measurements unless otherwise specified. Mean differences between active and historical control groups will be assessed and significance will be determined on the basis of a 95% CI. No formal estimate of the sample size has been made. This is an exploratory study and the number of patients was selected to enable an adequate clinical assessment of pharmacodynamic, safety, and tolerability parameters without presenting undue risk to a large number of patients.
Efficacy Analysis	Efficacy will be secondarily determined by summarizing success or failure to meet any of the primary or secondary endpoints as compared to Control treatment.
Safety Analyses	Safety data will be summarized for both treatment groups including frequencies and incidence rates. Safety will be assessed through monitoring of adverse events (AEs), serious adverse events (SAEs), chest CTs or chest X-rays, laboratory tests, oxygenation and ventilatory parameters, and vital signs.

Table 2: Schedule of Assessments and Procedures

	Screening	VentaProst - Day 1		VentaProst Days 2-10									End of Study
Study Procedures	**Within 14 Days Prior to Baseline**	**Baseline 0 Hr**	**12 hrs**	**D-2**	**D-3**	**D-4**	**D-5**	**D-6**	**D-7**	**D-8**	**D-9**	**D-10/ End Study Treatment**	**Day 28 (+/- 2 days)**
Written Informed Consent[1]	X												
Demographics	X												
Medical History	X												
Review Inclusion/Exclusion Eligibility Criteria	X	X											
Medication History/ Prior Meds	X												
Physical Examination	X												
Weight/Height[2]	X											X	
Randomization		X											
Chest CT Scan or CXR	X						X[3]						
Chemistry (including AST, ALT, AP, T. Bili) CBC , PT/PTT	X						X					X	
Pregnancy Test (Serum or Urine)	X												
COVID-19 diagnostic test such as molecular or antigen test	X												
Cardiac Troponin, and BNP	X						X					X	
Other blood tests: fibrinogen, ferritin, LDH, Triglycerides, D-Dimer, IL-6, ESR,CRP[4]	X						X					X	
Administer VentaProst		X	X	X	X	X	X	X	X	X	X	X	
Vital Signs[5]	X	X	X	X	X	X	X	X	X	X	X	X	
Oxygenation Measurements[6]		X	X	X	X	X	X	X	X	X	X	X	
Ventilator Parameters[7]		X	X	X	X	X	X	X	X	X	X	X	
AE/SAE Monitoring		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X
Prone position[8]		X	X	X	X	X	X	X	X	X	X	X	

[1] Informed consent may be obtained after screening study procedures that were conducted as a part of the patient's standard of care.

[2] Height only performed at screening

[3] Chest CT or CXR may be performed anywhere from 3-8 days as clinically warranted.

[4] These tests are collected only if available as Standard of Care

[5] Vital signs: Prior to initiating VentaProst, Days 1-10 twice daily (morning and evening) at the same time to reduce exposure to Health Care Professionals to include; temperature, pulse rate, blood pressure.

[6] Continuous SpO2 via pulse oximetry

[7] Ventilator Parameters will be collected twice daily along with vital signs and include: Ventilator Type, Ventilator Mode, FiO_2, Inspiratory Time, Mean Airway Pressure, Peak Inspiratory Pressure, Positive End Expiratory Pressure, Tidal Volume and Respiratory Rate

[8] Time Prone Position – 16 hours per day per OSU protocol

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LIST OF ACRONYMS, ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
Active	Inhaled epoprostenol administered via the VentaProst delivery system
AE	Adverse |Event
ALI	Acute Lung Injury
ALT (SGPT)	Alanine Aminotransferase (serum glutamic pyruvic transaminase)
AP	Alkaline Phosphatase
ARDS	Acute Respiratory Distress Syndrome
AST (SGOT)	Aspartate Aminotransferase (serum glutamic oxaloacetic transaminase)
bpm	Beats Per Minute
BNP	Brain Natriuretic Peptide
BUN	Blood Urea Nitrogen
cAMP	Cyclic Adenosine Monophosphate
CI	Cardiac Index (L/min/m^2)
CO	Cardiac Output (L/min)
Control	Inhaled 0.9% sodium chloride solution, USP administered via the VentaProst delivery system
CFR	Code of Federal Regulations
C_{max}	Maximum Concentration
CPB	Cardiopulmonary Bypass
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-Reactive Protein
CSR	Clinical Study Report
CNTS	Continuous Nebulization Tube Set
CVP	Central Venous Pressure (mm Hg)
DCF	Data Collection Form

Abbreviation	Term
DNR	Do Not Resuscitate
dPAP	Diastolic Pulmonary Arterial Pressure (mm Hg)
dSAP	Diastolic Systemic Arterial Pressure (mm Hg)
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
ESR	Erythrocyte Sedimentation Rate
ETT	Endotracheal Tube
FDA	Food and Drug Administration
FiO_2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
HME	Heat-Moisture Exchanger
HR	Heart Rate (bpm)
IABP	Intra-aortic Balloon Pump
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IL-6	Interleukin 6
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
LAR	Legally Authorized Representative
LDR	Lung Dosing Rate
LFT	Liver Function Test
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute
mPAP	Mean Pulmonary Arterial Pressure (mm Hg)
mSAP	Mean Systemic Arterial Pressure (mm Hg)
NC	Nasal Cannula
ng	Nanogram
OR	Operating Room
OTC	Over-the-Counter
PAH	Pulmonary Arterial Hypertension
PaO_2	Partial Pressure of Oxygen in Arterial Blood
PAP	Pulmonary Arterial Pressure (mm Hg)
PCWP	Pulmonary Capillary Wedge Pressure
PD	Pharmacodynamic
PEEP	Positive End Expiratory Pressure
PH	Pulmonary Hypertension
PIP	Peak Inspiratory Pressure
PK	Pharmacokinetic
PP	Per Protocol

Abbreviation	Term
PGI_2	Prostaglandin I_2 (epoprostenol)
PVR	Pulmonary Vascular Resistance (dyn/sec/cm^5)
RBC	Red Blood Cell (count)
RH	Right Heart
RHF	Right Heart Failure
RT-PCR	Reverse Transcription Polymerase Chain Reaction
RVSWI	Right Ventricular Stroke Work Index
SAE	Serious Adverse Event
SaO_2	Arterial Oxygen Saturation
sPAP	Systolic Pulmonary Arterial Pressure (mm Hg)
sSAP	Systolic Systemic Arterial Pressure (mm Hg)
SE	Standard Error
SOP	Standard Operating Procedures
SOC	Standard of Care
SpO_2	Oxygen Saturation by Pulse Oximetry
Study Drug	Active or Control Treatment
SVR	Systemic Vascular Resistance
TEAE	Treatment-Emergent Adverse Event
TEE	Transesophageal Echocardiogram
TPG	Transpulmonary Gradient
$t_{1/2}$	Half-Life
TLD	Total Lung Dose
ULN	Upper Limit of Normal
VA-ECMO	Veno-arterial Extracorporeal Membrane Oxygenation
VentaProst	VentaProst™ – Drug/device combination product consisting of aerosolized epoprostenol delivered via dedicated drug delivery system
VentaProst Nebulizer	The nebulizer assembly that is part of the VentaProst delivery system
VTE	Venous Thromboemobolism
VV ECMO	Venovenous Extracorporeal Membrane Oxygenation
WBC	White Blood Cell (count)
WHO	World Health Organization

2.1 Introduction

COVID-19 is a rapidly emerging pathogen that has recently been declared a pandemic by the World Health Organization (WHO). No targeted therapeutic treatments for coronavirus (COVID-19) have been identified. Symptoms range from mild upper respiratory tract infection to profound hypoxia, severe pneumonia, ARDS and death. Progression of end stage disease is unpredictable with high fatality rates in mechanically ventilated patients as a result of multi-organ failure. Among patients who require hospitalization, mortality may be 5% to 15%, and for those who become critically ill, reported mortality ranges from 22% to 62%.

Prostacyclin therapy—available in oral, inhaled, and intravenous forms—is an analogue which mimics endogenous prostacyclin (PGI2). Prostacyclin binds to its receptor (a G-protein coupled receptor) found on the surface of vascular smooth muscle and platelets, activates cyclic adenosine monophosphate (cAMP), and results in inhibition of platelet aggregation, vascular smooth muscle relaxation and vasodilation of the pulmonary arteries (Mitchell, Ali et al. 2008). Prostacyclins are most commonly used in the treatment of PAH due to their potent vasodilatory effects. In addition, prostacyclin analogs also inhibit platelet aggregation and may reduce prothrombotic effects of endothelin.

The rationale for use of vasodilators in COVID-19 patients rests on their rapid local effect on the pulmonary vasculature, which has shown to lead to increased oxygenation in other diseases, such as PAH (Higenbottam, Wheeldon et al. 1984) and post-surgical PH (De Wet, Affleck et al. 2004). Epoprostenol has the additional advantage over inhaled nitric oxide in that it may be directly administered through a standard ventilator (closed-circuit).

The rationale for aerosolized prostacyclin use in COVID-19 patients experiencing hypoxia leading to cardiac failure is two-fold:

(1) inhaled prostacyclin therapy has been used in the treatment of ARDS and has been shown to improve oxygenation and ventilation-perfusion mismatch (see Section 9). Prostacyclins, such as epoprostenol, promote pulmonary vasodilation via a cyclic adenosine monophosphate-mediated decrease in intracellular calcium (Figure 4). While it has not been associated with improved outcomes, such as mortality, and it's use in ARDS is off-label, it may be used in severe life-threatening hypoxemia refractory to conventional ARDS management, such as has been seen in COVID-19.

(2) The second potential benefit of prostacyclin therapy in the management of COVID-19 is to mitigate direct SARS-CoV-2-associated coagulopathy. Prostacyclins have anti-inflammatory (Dewachter 2012) and antiplatelet aggregation properties[1]. Microvascular thrombosis and large vessel venous thromboembolism have been described anecdotally and in case reports of corona virus infected patients and abnormal coagulation parameters are associated with increased mortality (Giannis, Ziogas et al. 2020). Inhibition of platelet aggregation occurs with prostacyclin therapy and may mitigate thrombosis in situ seen in PAH itself, and potentially in patients with COVID-19 associated respiratory illness.

Literature data with both inhaled NO and inhaled epoprostenol in ARDS, acute lung injury and severe hypoxemia show improvement of oxygenation (Afshari, Bastholm Bille et al. 2017), (Dzierba, Abel et al. 2014), decrease of pulmonary arterial pressure (Fuller, Mohr et al. 2015) and in some cases improvement in clinical outcomes such as shorter time on mechanical ventilation and shorter time in ICU (Ammar, Bauer et al. 2015). However, due to the heterogeneity of the population and the severity of the disease, not all studies agree on the effectiveness of inhaled epoprostenol, particularly to reduce mortality in ARDS (Adhikari, Dellinger et al. 2014), (Afshari, Bastholm Bille et al. 2017). Meta-analyses have concluded that the quality of the currently published data for the use of inhaled vasodilators in ARDS, ALI and refractory hypoxemia is insufficient to definitely conclude for or against their use (Afshari, Bastholm Bille et al. 2017), (Fuller, Mohr et al. 2015).

This study will evaluate the potential therapeutic benefit of VentaProst in treating patients with COVID-19 at risk for the progression of respiratory and/or cardiac/circulatory failure. This double-blind, placebo controlled study will assess the efficacy and safety of VentaProst at a range of 3.4-30.6 ng/kg/min for a maximum of 10 days at the discretion of the Investigator. The patient will be followed through Day 28 to assess their clinical status.

2.2 VentaProst

2.2.1 Nonclinical Experience

Refer to the current Investigator's Brochure (IB) for details of nonclinical pharmacology and toxicology studies with VentaProst.

2.2.2 Clinical Experience

There have been no clinical trials to date with VentaProst in COVID-19 patients (see Section 2.2.4 below for summary of clinical data with VentaProst in cardiac surgery patients).

2.2.3 Summary of Pharmacokinetic Results

Epoprostenol undergoes rapid chemical hydrolysis under physiological conditions to yield 6-keto-PGF1α and is also subject to enzymatic degradation. As such, it is only possible to evaluate the PK using radioactively labeled drug. Studies using 3H-epoprostenol sodium indicate half-life is generally less than 3 minutes with an I.V. bolus, and with I.V. infusion, plasma steady-state concentrations were achieved within 15 minutes of initiation of the infusions, and steady-state concentrations increased linearly with increasing infusion rate. Tissue distribution studies indicate the highest levels of radioactivity were observed in the kidney, liver, and small intestine and the lowest levels were observed in brain and adipose tissue. Epoprostenol-derived material is rapidly excreted into urine and feces after dosing with epoprostenol sodium.

There is only one study in the literature that reports the PK of inhaled epoprostenol. The study by Haraldsson (Haraldsson, Kieler-Jensen et al. 2000) was designed to evaluate the effects of inhaled epoprostenol on platelet aggregation after surgery. No differences were seen in 6-keto-PGF1α levels with two dose levels of epoprostenol compared to placebo

over six hours of administration in the ICU. Epoprostenol deposition in the lungs was not quantified, but the aerosol was administered only during the inspiratory phase of mechanical ventilation. The blood levels of 6-keto-PGF1α by enzyme immunoassay in this study were reported to be several times higher than other levels reported in the literature.

In 2017, Stanford University's Department of Cardiac Surgery conducted an observational study (IND129777, Report# APC-VP-CLN-004) investigating the levels of 6-keto-PGF1α in cardiac surgery patient requiring CPB. Sixteen patients were enrolled; eight did not received inhaled epoprostenol, eight received aerosolized epoprostenol at a nominal starting dose of 50 ng/kg/min.

Plasma levels determined in aerosol epoprostenol naïve patients indicates that cardiac surgery procedures, including CPB, result in elevated endogenous levels of both 6-keto-PGF1α and thromboxane B2. Delivery of aerosol epoprostenol in patients resulted in a further elevation of 6-keto-PGF1α levels, but not thromboxane B2.

While it proved difficult to delineate the endogenous and exogenous contributions of aerosol delivery during surgery, 6-keto-PGF1α levels declined rapidly in aerosol naïve patients during ICU stay. Examination of the 6-keto-PGF1α levels during weaning, after this endogenous decline, indicate that the overall aerosol delivery efficiency, nebulized to absorbed (deposited lung dose), is less than 8%. That is, out of a nominal dosing rate of 50 ng/kg/min only 4 ng/kg/min actually reaches the lungs and gets absorbed.
Comparison to recently published data (Nicolas, Krause et al. 2012) investigating 6-keto-PGF1α levels during steady state I.V. administration of Flolan indicates that the systemic exposure from aerosol delivery in cardiac surgery is similar to, or lower, than that experienced from intravenous administration of the approved Flolan product.

The findings of this observational PK study with inhaled epoprostenol are sufficient to make a correlation to historical systemic exposure levels with intravenous administered Flolan (the reference listed drug) and show levels of exposure similar to, or lower than, the currently approved intravenous product.

2.2.4 Summary of Clinical Results

The safety and tolerability of VentaProst were evaluated in a Phase 2a Clinical Study in cardiac surgery patients "*A Two-Part Pharmacodynamic Study to Compare VentaProst™ (Epoprostenol Solution for Inhalation via Custom Drug Delivery System) Dosing to Conventionally Administered Aerosolized Epoprostenol Dosing in Cardiac Surgery Patients*" (NCT03122730).

Overall, 15 patients were exposed to doses of VP from 3.4 to 20.4 ng/kg/min in this study. Administration of VP in this dose range was well-tolerated. Overall, there were 2 patients (28.6%) in Part I and 1 patient (12.5%) in Part II who experienced a total of 7 TEAEs. All 7 TEAEs were assessed by the investigator as related to the surgical procedure and as unrelated to the study drug and unrelated to the device. No deaths occurred during the study. A total of 3 patients had 1 SAE each. All 3 SAEs were considered to be unrelated to the study drug or the study device.

Seven patients were evaluated in Part I to determine the effective dose equivalence between VP delivered at 17 ng/kg/min and off-label aerosolized Veletri administered at 50 ng/kg/min during mechanical ventilation. In all patients, VP 17 ng/kg/min was found to be equivalent either by calculation of effect compared with aerosolized Veletri 50 ng/kg/min or the investigators' judgement. In most patients, no differences were observed in oxygen saturation ranges between VP and aerosolized Veletri treatments at the same FiO2 while on the ventilator. The investigator determined that oxygenation, assessed by oxygen saturation measurements, did not change disproportionately with ventilator operating parameters on VP compared with aerosolized Veletri.

Eight patients were evaluated in Part II of the study to identify the optimal dose of VP. In the investigator's judgement, the optimal VP dose was determined to be 6.8 ng/kg/min in 2 patients, 10.2 ng/kg/min in 3 patients, and 13.6 ng/kg/min in 3 patients, which is the minimal dose that reliably produced a maximum hemodynamic response in all patients.

There have been no clinical trials to date with VentaProst in COVID-19 patients.

See IB for additional clinical information regarding inhaled epoprostenol.

2.2.5 Summary of Known and Potential Risks of Inhaled Epoprostenol Administration

Safety of inhaled epoprostenol in cardiothoracic surgery patients is remarkable. In the reported literature to date, there were no reports of serious or life-threatening drug-related safety events. Due to its mechanism of action, inhaled epoprostenol may theoretically cause increased bleeding (anti-platelet mechanism) or systemic vasodilation consequent to spill over into the central circulatory system, but no such events have been reported. Some accounts of the use of inhaled prostacyclin in the chronic setting (e.g. iloprost for PAH) report transient events as listed on the approved product labeling. These include cough, headache, flushing, and an influenza-like syndrome. However, these types of events are unlikely to be reported due to sedation in the ICU setting.

VentaProst may result in hypotension, which will be monitored via frequent - assessments of oxygenation, ventilatory and hemodynamic parameters and vital signs. Pulmonary edema and pulmonary bleeding are potential risks due to the drug's mode of action (refer to Section 7.2.2). Worsening oxygenation is a theoretic concern through worsened ventilation/ perfusion matching. This will be monitored through continuous pulse oximetry throughout the administration of the inhaled epoprostenol.

Risks to subjects in this study are related to common procedures performed (e.g., venipuncture) and the documented adverse events (AEs) listed in the current Investigator's Brochure. These risks are communicated to the subjects in the consent forms. There may be additional risks that are currently unknown.

The benefits of the study may include targeted lung vasodilation and improved oxygenation, potential anti-platelet effects on the lung vasculature, reduction in disease progression, avoidance of greater oxygen needs and early weaning off mechanical ventilation. If the drug does have such properties, then this may aid recovery, improve outcomes and enable an earlier discharge from the hospital.

There is no funding awarded to the patients participating in this study.

2.2.6 Dosing Rationale for VentaProst

Literature on the current use of aerosolized epoprostenol in cardiac surgery and in ARDS shows a wide range and technically variable dosing for lowering PVR (Rao, Ghadimi et al. 2018), (Kallet, Burns et al. 2017), (Fuller, Mohr et al. 2015). Most of the experience is with continuous nebulization by commercially available nebulizers in various positions in mechanical ventilator circuits at doses of 50 ng/kg/min. Unlike the commercially available nebulizer systems, the VentaProst delivery platform aerosolizes epoprostenol only during the inspiratory cycle of the ventilator and administers respirable sized aerosol droplets (3-5 μm) in close proximity to the ETT of mechanically ventilated patients.

The assumed effect of the current continuous dosing regimen of 50 ng/kg/min is that the hemodynamic response is maximized and that no further improvements would be seen by increasing the dose. The initial in vitro estimate of the equivalent VentaProst (VP) dose to a 50 ng/kg/min conventional dose of continuously aerosolized Veletri was 17 ng/kg/min, which was the starting dose in Part I of the APC-VP-CLN-001 Phase 2a study conducted by Aerogen Pharma. During Part I of the study, it was determined that this dose is equivalent to 50 ng/kg/min epoprostenol delivered off-label via a generic nebulizer and continuous delivery. In Part II of the APC-VP-CLN-001 Phase 2a study, the VP dose escalation started from an initial dose of 3.4 ng/kg/min (20% of the equivalent dose). The dose was then increased in 3.4 ng/kg/min increments. Part II of the study was designed to demonstrate that the dose-response plateau could be achieved using lower VP doses than the initial estimated equivalent dose in Part I. Doses up to 30.6 ng/kg/min were approved for use in the study. In Part I of the study one patient, per the investigator discretion, received a 20.4 ng/kg/min dose. In Part II of the study it was determined that the optimal VP dose of 6.8 ng/kg/min in 2 patients, 10.2 ng/kg/min in 3 patients, and 13.6 ng/kg/min in 3 patients provided stable hemodynamic response. Based on these data, the recommended starting dose of VP, will be 13.6 ng/kg/min, as this dose is anticipated to produce the maximum hemodynamic response.

The proposed nominal dosing regimen for this COVID-19 trial is for up to 10 days of breath-synchronized aerosol delivery with a starting dose of study drug 13.6 ng/kg/min. Based on hemodynamic and oxygenation parameters, the dose can be titrated in 3.4 ng/kg/min steps up to a maximum of 30.6 ng/kg/min or down to a minimum of 3.4 ng/kg/min while patients are on mechanical ventilation. Of this nominal dosing rate approximately 30% will reach and deposit in the lung. Thus, the maximum Lung Dosing Rate (LDR) is ~10 ng/kg/min and the maximum Total Lung Dose (TLD) is ~ 144 μg/kg (Refer to VP IB Edition 6 dated 17-Jun-2020).

The inhalation toxicology program for VentaProst, originally designed for the cardiac surgery indication, covered a maximum LDR of 320 ng/kg/min and 60 ng/kg/min and a maximum TLD of 1091.4 μg/kg and 172.8 μg/kg in rats and dogs respectively. The LDR and TLD margins over the proposed maximum clinical exposure are thus 32 and 6, and 7.6 and 1.2, in rats and dogs respectively.

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is the reduction of respiratory, cardiac or circulatory failure in patients with confirmed COVID-19.

3.2 Secondary Objectives

The secondary objective in this study is to evaluate the effects of VentaProst on improvement in oxygenation, improvement in clinical outcomes and safety and tolerability.

The study will also evaluate the effects of VentaProst on inflammatory parameters in subjects with confirmed COVID-19.

3.3 Study Design

This is a double-blind, placebo controlled study of VentaProst (Active) as compared to placebo (Control). Active is inhaled epoprostenol administered via the VentaProst delivery system in 10 COVID-19 positive patients. Control is inhaled 0.9% sodium chloride solution administered via the VentaProst delivery system in 10 COVID-19 positive patients. Throughout the remainder of the protocol both Active and Control will be referred to as "study drug". This study will evaluate the potential therapeutic benefit of VentaProst in treating patients with COVID-19 who require mechanical ventilation and are at risk for the progression of respiratory and/ or cardiac/circulatory failure. This study will assess the efficacy and safety of VentaProst at an initial dose of 13.6 ng/kg/min (A range from 3.4-30.6 ng/kg/min may be administered as clinically required for a maximum of 10 days at the discretion of the Investigator. Patients will be followed through Day 28 to assess clinical outcomes.

Patients will be consented and randomized to either the Active or Control group within 48 hours of being placed on mechanical ventilation. Informed consent may be obtained after some screening study procedures were collected as part of the patient's standard of care treatment. Patients will be administered study drug using the VentaProst delivery system which allows up and down titration of study drug to achieve hemodynamic and oxygenation stability. The starting dose of study drug will be initiated at 13.6 ng/kg/min. Based on hemodynamic and oxygenation parameters, the dose of study drug can be increased in 3.4 ng/kg/min increments up to a maximum of 30.6 ng/kg/min or down to a minimum of 3.4 ng/kg/min.

All study staff with the exception of the unblinded pharmacist and Sponsor CRA will be blinded to which treatment regimen a patient has been assigned. Titration and weaning will be performed the same for all patients. Study drug will be administered based on the pump rate calculated for active treatment in mL/hr. Titration guidelines are provided in Section 5.3.3 and Table 3.

3.4 Duration of Participation

Patients who meet entry criteria will be entered into the study and the duration of study participation for each patient is listed below. The duration of study participation for each patient is as follows:

- Screening: up to 14 days

- Treatment: up to 10 days
- Follow up: 28 days

4. SELECTION AND WITHDRAWAL OF PATIENTS

Approximately 20 COVID-19 positive patients requiring mechanical ventilation will be enrolled in this study. Ten study participants will be randomized to either Active (inhaled epoprostenol administered via the VentaProst delivery system) treatment or Control (inhaled 0.9% sodium chloride solution administered by the VentaProst delivery system at calculated rates (mL/hr) used for the aerosolized epoprostenol). Study drug will indicate both Active and Control treatments.

Patients who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to enroll into the study.

4.1 Inclusion Criteria

Patients are eligible for this study if they meet all of the following criteria:

1. Women and Men Age ≥18 years old (no upper limit)
2. Confirmed COVID-19 positive by a diagnostic test such as molecular or antigen test
3. Patients who require invasive mechanical ventilation.
4. Enrolled into study within 48 hours of being placed on mechanical ventilation
5. Consent or professional consent obtained
6. Duration of shortness of breath must be within the previous 14 days.
7. Female subjects of childbearing potential must have a negative pre-treatment pregnancy test (serum or urine).
8. Received or currently receiving dexamethasone therapy for COVID-19
9. Willing and able to comply with treatment schedule and follow-up.

4.2 Exclusion Criteria

Patients are **NOT** eligible for this study if they meet any of the following criteria:

1. Patients on ECMO support.
2. Patients receiving another inhalation research medication or inhaled nitric oxide.
3. Not expected to survive for 48 hours.
4. Pregnant (positive pregnancy test in a pre-dose examination) or breastfeeding
5. Open tracheostomy.
6. Clinical contra-indication, as deemed by the attending physician.
7. Allergy to Epoprostenol and its diluent
8. Using inhaled vasodilators at baseline.
9. Patients who are hemodynamically unstable as determined by investigator

10. Patients with significant hemoptysis as determined by investigator

4.3 Re-Screening of Patients

Patients may not be enrolled more than once.

4.4 Removal of Patients from Therapy or Assessment

Aerogen Pharma or the Investigator may discontinue patients from the study at any time for safety or administrative reasons.

The End of Treatment Study procedures (Day 10) are to be completed for all patients who discontinue from the study prior to Day 10 (except Screen Failure patients).

The Investigator will promptly explain to the patient or their LAR that the study will be discontinued for the patient and provide appropriate medical treatment and other necessary measures for the patient.

Patients who discontinue early from the study will be discontinued for one of these primary reasons: Adverse events, patient death, lost to follow-up, patient withdrew consent, protocol violation, lack of efficacy, investigator decision, study terminated by sponsor, screen failure, or other. Study disposition information will be collected on the Patient Disposition DCF.

4.4.1 Criteria for Stopping VentaProst Treatment

Individual patients stopping criteria: At any time during study drug administration , patients may be removed from study treatment and placed on standard of care (SoC) therapy if they meet one or more of the following pre-defined criteria leading to a deterioration in their condition:

- Severe hypotension as evidenced by a systolic BP < 90 mmHg or MAP < 60 mmHG for >2 hours from the start of VentaProst
- Need for VV ECMO
- Need to increase existing vasopressor therapy by more than 25%
- Worsening oxygenation, ventilatory, or hemodynamic parameters that in the opinion of the investigator the patient should be removed from study treatment
- Massive hemoptysis thought to be clinically significant and not due to endotracheal tube trauma
- Pulmonary Edema

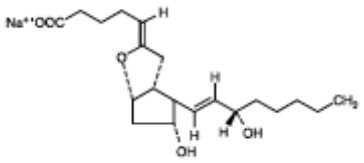
Study stopping criteria: If 3 patients are removed from the study for any of the above conditions, the study will stop further enrollment and investigation will be conducted to determine the cause of the events. An independent safety evaluation will also be conducted. If it is suspected that the investigational product has caused the events, the study will be terminated.

Independent Safety Evaluation: Independent safety evaluation will be conducted by a licensed physician who is not involved in the VentaProst COVID-19 clinical study or the sponsoring organization.

5. STUDY TREATMENTS

5.1 Identity of Medication Component of the Investigational Product

The study medication VentaProst, Flolan (epoprostenol sodium), is manufactured by GlaxoSmithKline and has been analyzed and released according to their specifications. The labelling of Flolan and placebo for this clinical trial will follow the protocols and procedures set forth by OSU's Investigational Drug Services (IDS). The Control for this study is 0.9% sodium chloride solution, USP from the OSU IDS stock and will be labeled in a blinded manner per the IDS protocols for maintenance of study blind.

Drug Substance Name	Epoprostenol Sodium
Chemical Name	5Z,9α,11α,13*E*,15*S*)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-1-oic acid.
Molecular Formula	$C_{20}H_{31}NaO_5$
Structural Formula	
Molecular Weight	374.45

5.1.1 Storage Condition

Both the vials of study medication and sterile diluent buffer should be stored between 20º to 25ºC (68º to 77ºF) with excursions permitted to 15° to 30°C (59° to 86°F) and kept in the supplied carton to protect the product from light. Study medication will be stored in a secure, controlled-access location at the study sites.

The 0.9% sodium chloride solution will be stored according the product labelling.

5.2 Treatments Administered

Patients will receive study drug via mechanical ventilator, starting at 13.6 ng/kg/min. If determined by the treating physician, study drug can be up titrated in 3.4 ng/kg/min increments to a maximum of 30.6 ng/kg/min or down to a minimum of 3.4 ng/kg/min. At the Investigator's discretion, the patient will be weaned off the drug in 3.4 ng/kg/min increments. Study drug will be administered based on the pump rate calculated for the active treatment but delivered in mL/hr. Study drug can be administered up to 10 days.

5.3 Study Medication Supply, Preparation, and Administration

5.3.1 Study Medication Supply

The medicinal component of VentaProst, Flolan, (epoprostenol sodium), is already approved for I.V. delivery. The dosage form is a vial of 1.5 mg epoprostenol as a lyophilizate and the required pH 12 Sterile Flolan diluent per the currently approved packet insert (NDA20-444/ Supplement 24[1]). Flolan and its diluent (pH 12 Sterile Diluent) are not re-formulated by Aerogen Pharma. Flolan is used with the same diluent system and reconstituted per the approved packet insert.

Flolan and diluent container closure (glass vial and stopper/crimp-pH 12 Sterile Diluent for Flolan comes in a plastic bottle for mixing) and secondary packaging (cardboard box) are not being altered, including the information on the vial and box label and the information in the approved Flolan packet insert. This preserves the approved drug labeling information per NDA 20-444.

Placebo will be a corresponding volume of 0.9% sodium chloride solution from the OSU IDS stock.

5.3.2 Study Medication Preparation

Refer to the VentaProst-COVID Pharmacy Manual for preparation of study drug solution..

Prior to use, drug solutions must be protected from light and refrigerated at 2° to 8°C (36° to 46°F) if not used immediately. Do not freeze drug solutions and discard any drug solution that has been frozen. Discard any drug solutions if refrigerated for more than 8 days. Control, (0.9% sodium chloride solution) will be placed in identical syringes and masked according OSU IDS procedures for blinded studies.

5.3.3 Study Medication Administration

In the ICU, patients will be started on study drug administered via the VentaProst delivery system at an initial dose administered at 13.6 ng/kg/min. Study Drug Study drug may be titrated up or down in 6.8 ng/kg/min increments (refer to VentaProst Pharmacy Manual) as clinically indicated to a dose range of 3.4 - 30.6 ng/kg/min. Study drug will be administered based on the pump rate calculated for the active treatment in mL/hr. Study drug can be administered up to 10 days.

[1] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020444s024lbl.pdf

Table 3: Administration Titration Guidelines*

Up titration Guideline	Downward Titration / Guideline
Start Dose: 13.6 ng/kg/min	Start Dose: 30.6 ng/kg/min
1st Step Up Dose (17.0)	1st Step Down dose (23.8)
2nd Step Up Dose (20.4)	2nd Step Down Dose (17.0)
3rd Step Up Dose (23.8)	3rd Step Down dose (10.2)
4th Step Up Dose (27.2)	4th Step Down dose (3.4)
5th Step Up Dose (30.6)	

*All study drug will be administered per the calculated pump rate for the active treatment in ml/hr

Table 4-Example of Up Titration for male with Ideal Body Weight of 70 kg

Initial Dose Rate	Initial Pump Rate	New Dose Rate	New Pump Rate
13.6 ng/kg/min	1.89 mL/hr	13.6 ng/kg/min	1.89 mL/hr
		17.0 ng/kg/min	2.39 mL/hr
		20.4 ng/kg/min	2.86 mL/hr
		23.8 ng/kg/min	3.33 mL/hr
		27.2 ng/kg/min	3.81 mL/hr
		30.6 ng/kg/min	4.28 mL/hr

Active drug is prepared with 50 mL in each syringe at a concentration of 30,000 ng/mL.
All study drug will be administered per the calculated pump rate for the active treatment in ml/hr.

5.3.4 Study Medication Weaning

Patients will be weaned from study drug slowly to avoid rebound vasoconstriction. During weaning, doses will be decreased in steps of 6.8 ng/kg/min increments, with a no less than 5 minutes between changes as clinically indicated. The weaning process should occur in isolation to other treatment changes (no changes in inotropes, vasopressors, or vasodilators) whenever possible. Patients will be observed closely before, during, and after dose changes. In the event patients demonstrate signs of hemodynamic instability or a decrease in oxygenation indicated by pulse oximetry during downward titration, the dose will be returned to its previous level. Once patients have been stable for at least 15 minutes, repeat attempts at dose reduction may be undertaken. The process will continue until patients are fully weaned. Patients will be monitored for safety and efficacy throughout study drug administration.

5.4 Identity of the Device Component of the Investigational Product

5.4.1 Identity of Device

The Phase 2a VentaProst drug delivery system is designed to accurately and precisely administer aerosol to the lungs of critically ill patients who require support via mechanical ventilation. The aerosol generator's fundamental operating mechanism and materials of construction will be similar to the 510(k)-cleared Aeroneb Solo System (K120939, K103635, K070642, Aerogen Ltd) and it is being designed for compatibility with the range of ventilators found in the OR and ICU.

5.4.1.1 VentaProst Aerosol Delivery to Ventilated Patients

The VentaProst delivery system (Figure 1) consists of reusable and single-patient use disposable elements:

1. Reusable multi-patient use components consist of two electronic controllers with power supplies, Aerogen Solo Nebulizer Cable, and Sensirion Flow Sensor Cable. When used together, they synchronize aerosol generation with the patient's inspiratory pattern through a single-patient use, disposable administration kit.
    - Aerogen Pro-X, is a commercially available device (K120939[2]) cleared for use to continuously operate the disposable Aerogen Solo nebulizer. (item #1 Figure 1).
    - Aerogen Pharma Controller (AP Controller) is an investigational device, which synchronizes aerosol generation with the ventilator inspiratory cycle (item #2 on Figure 1). This controller was tested to demonstrate its safety for use under IND129777.
    - Aerogen Solo Nebulizer Cable
    - Sensirion Flow Sensor Cable
2. Single-patient disposable kit:
    - Aerogen Solo nebulizer (item #3 on Figure 1) is a commercially available, low mass and low profile vibrating mesh aerosol generator (K070642) cleared for use with the Aerogen Pro-X controller and Aerogen Continuous Nebulization Tube Set (CNTS).
    - Aerogen CNTS and syringe (items #4 and 5 on Figure 1) is a commercially available device (K103635) cleared for use to connect to the Aerogen Solo and deliver medication from the drug reservoir (syringe) to the mesh the nebulizer.
    - Flow sensor and cable connected to the Aerogen Pharma Controller (AP Controller, item #7 on Figure 1). This is a new component of the system, which was tested to demonstrate safety for use in a clinical study.

The VentaProst delivery system will be used in conjunction with a commercially available and FDA-cleared syringe pump (item #8 on Figure 1). In general, any available syringe pump, which (1) is compatible with the Aerogen Continuous Nebulization Tube Set (CNTS syringe and tubing), and (2) is capable of delivering medication to the vibrating mesh nebulizer within the range of 0.4 to 12.0 mL/h as required to deliver the doses specified in the APC-VPCOV-CLN-001 Pharmacy Manual. For purposes of the VPCOV study, Aerogen Pharma will supply the Perfusor® Space Infusion Syringe Pump System from B.Braun (Figure 1). This particular syringe pump is FDA-cleared (K093913), it is compatible with the CNTS syringe (items #4 on Figure 1) and is able to

[2] The product names for the Aerogen commercial products changed from the term "***Aeroneb***", to the brand name "***Aerogen***". A Note to File was submitted to FDA and receipt was acknowledged by the Branch Office

deliver fluids in the rage of 0.4 to 12.0 mL/h. It is worth noting that on 11 April 2020, this pump received EUA for use in the tracheal delivery of continuous nebulized medications into a nebulizer to treat patients of all ages with or suspected of having the Coronavirus Disease 2019 (COVID-19)[3].

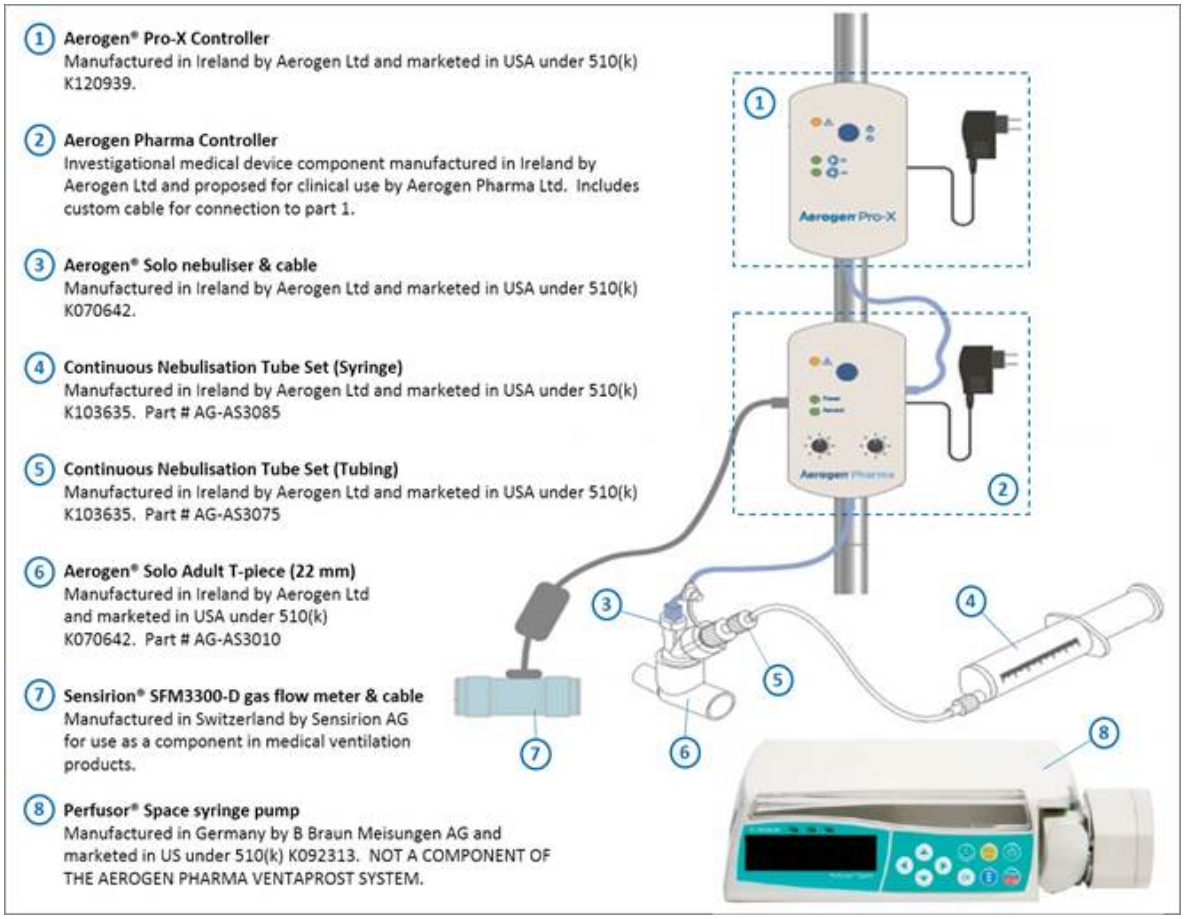


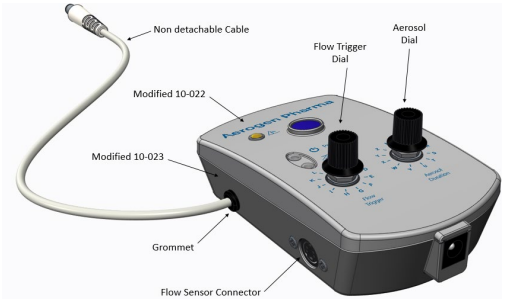
Figure 1: Drug Delivery System

The Aerogen Pro-X (item #1, Figure 1), Aerogen Solo (item #3, Figure 1) are mounted on an I.V. pole at the patient's bedside. The two controllers and Aerogen CNTS (items #4 and 5, Figure 1) are routinely used as a system within their intended use. The sensor and nebulizer are connected into specific locations of the inspiratory limb of the ventilator pre- and post the humidifier, respectively (see Figure 2). The addition of the AP Controller and an off-the shelf Sensirion flow sensor enables the VentaProst system to synchronize aerosol delivery with the inspiratory cycle of the ventilator (Figures 1 and 2).

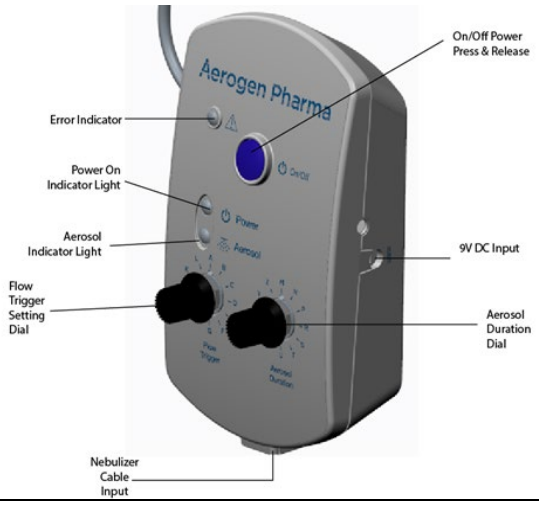
[3] https://www.fda.gov/media/136894/download

Figure 2 illustrates the AP Controller, which is similar to the commercially available Aerogen Pro-X controller in form, size, weight and materials used for the upper and lower shells. The AP Controller uses the same AC/DC adapter and cable as used in the commercial Aerogen Pro-X controller. The packaging used for the AP Controller is same as packaging validated by Aerogen Ltd. for the commercially available Aerogen Pro-X system. Functionality of the AP Controller was tested in design verification studies (IND129777). Two dials (Figure 2) are used to: (1) set the flow threshold for nebulization triggering during the inspiratory cycle of the ventilator, accommodating initial ventilator baseline bias flows, and (2) set the duration of nebulization during the inspiratory cycle (a detailed description of the mechanism of action of the AP Controller is presented in IND129777).

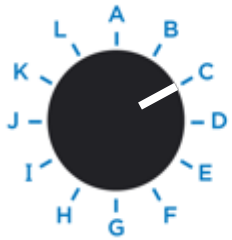
A. Diagram of Aerogen Pharma Controller (left side view)



B. Diagram of Aerogen Pharma Controller (right side view)

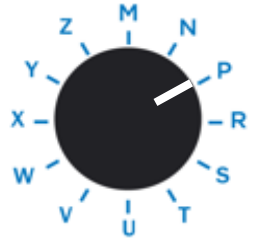


C. Flow Trigger Dial settings



A	2.5slm
B	4.0slm
C	5.5slm
D	7.0slm
E	8.5slm
F	10.0slm
G	11.5slm
H	13.0slm
I	14.5slm
J	16.0slm
K	17.5slm
L	19.0slm

D. Aerosol Duration Dial settings



M	0.3sec
N	0.4sec
P	0.5sec
R	0.6sec
S	0.7sec
T	0.8sec
U	0.9sec
V	1.0sec
W	1.1sec
X	1.2sec
Y	1.3sec
Z	1.4sec

Figure 2: Aerogen Pharma Controllers

Prior to administration, study drug will be prepared per the VP COVID Pharmacy Manual and placed into a 60 mL CNTS syringe. The syringe will be labeled to maintain the study blind. The user will attach the syringe to the CNTS tubing and prime the tube set so that the formulation reaches the Aerogen Solo, producing aerosol generation. The CNTS syringe set will be placed in a B Braun Perfusor Space Infusion syringe pump. The 15-mm T-Piece with nebulizer is placed between the ventilator circuit and the ETT (Figure

2). The user will select the pump rate (mL/hr) to deliver the recommended dose based on the ideal body weight in kilograms (kg) dispensed to achieve the dose rate in ng/kg/min for active treatment. The control treatment's corresponding pump flow rate in mL/hour will be calculated based on initial dose of Flolan in ng/kg/min. All study drug will be administered per the calculated pump rate for active treatment in ml/hr. The user will be able to adjust this recommended dose up or down (per protocol) by changing pump rate prior to selecting dose and initiating delivery. The selected dose will then be dispensed by the pump to the receiving surface of the mesh, resulting in generation of an aerosol with a volume median diameter in the range of 2 to 5 µm. The Aerogen Pharma Controller monitors the patient's breathing pattern and user adjusts the knob (on left) to initiate aerosol generation at the beginning of the breathing cycle. The knob on right sets the duration of aerosol generation within each breath.

The VentaProst device is designed to be compatible with standard intensive care unit (ICU) equipment. The following site-specific equipment will be needed to deliver the therapy: B.Braun syringe pump (provided by Aerogen Pharma), ventilator, endotracheal tube (ETT), humidifier, ventilator circuit. This equipment is standard for critical care medicine.

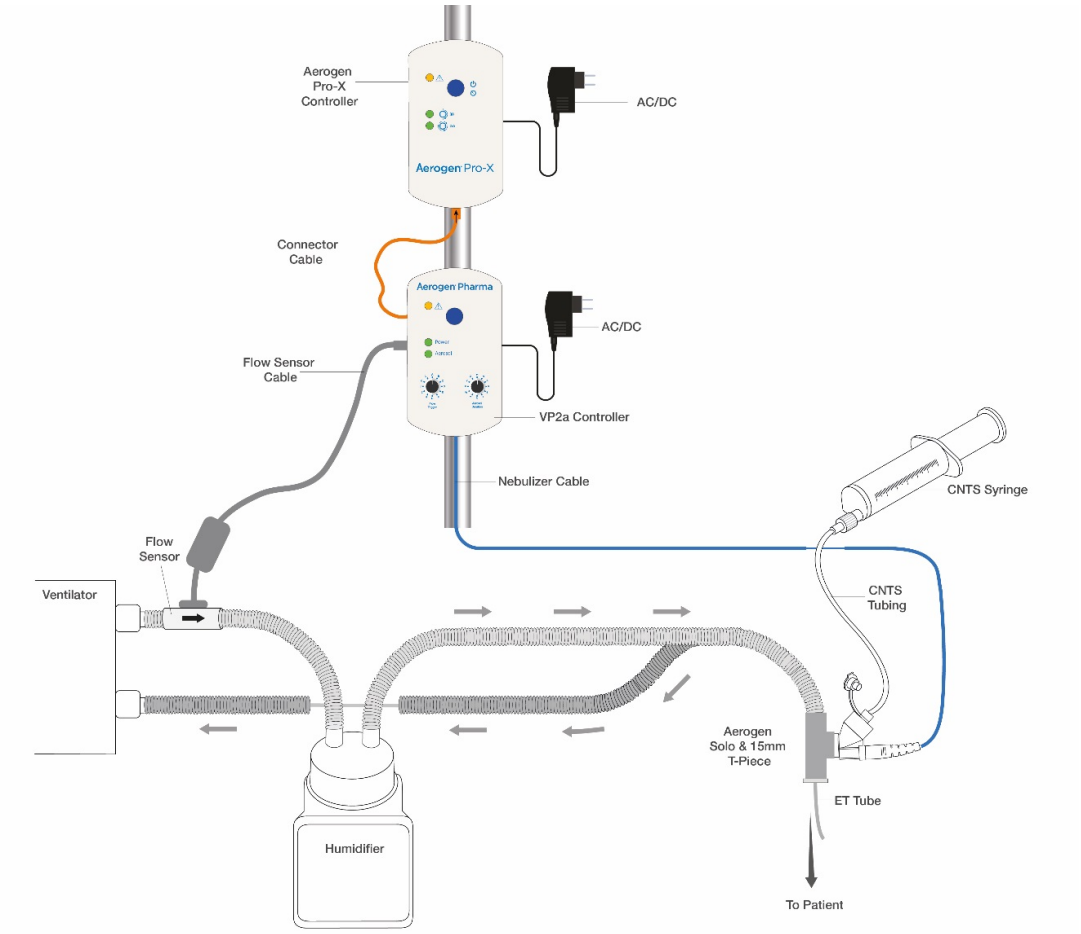


Figure 3 - VentaProst Device Placement in the Gas Pathway

5.4.2 Ventilator Settings

The device is designed for use with standard adult ventilator settings. An intermittent positive pressure ventilatory mode (i.e., not constant positive airway pressure [CPAP] or t-piece) is required to activate the device to deliver aerosol during the inspiration phase. A Heat-Moisture Exchanger (HME) may be used in the device circuit.

The site will utilize OSU's Standard of Care (SOC) mechanical ventilation guidelines for care of patients for COVID-19 with ARDS. The following ventilator parameters will be assessed daily while on VentaProst: Ventilator type, Mode, FiO_2, Inspiratory Time, Mean Airway Pressure, Peak Inspiratory Pressure, Positive End Expiratory Pressure, Respiratory Rate and Tidal Volume.

5.4.3 Device Supply

All device supplies will be provided by Aerogen Pharma Limited (including the B.Braun Syringe Pump). The serial numbers for the controllers, flow sensor, and nebulizer will also be recorded in an IP accountability dispensing log.

Used and unused devices will be inventoried and returned to the Sponsor or Sponsor's designee.

5.4.4 Device Replacement

Devices may be replaced at any time if there a suspicion of malfunction, but must be replaced if:

- The investigator suspects that, due to device malfunction, less than 90% of the total dose of study drug has been delivered. Reduced doses must be estimated and recorded in the patient's medical record and source documentation.
- The investigator suspects the device is not performing optimally for any reason.

5.4.5 Device Malfunction or Failure

One device (Aerogen Pro-X controller, Aerogen Pharma Breath Controller, Flow Sensor, Solo nebulizer, CNTS tubing and syringe, and associated components) is expected to perform throughout the duration of study treatment. If the controllers, Flow Sensor, CNTS tubing and syringe, or the Solo nebulizer are not functioning optimally for any reason, instructions for trouble-shooting provided in the device instruction for use manual should be followed. If one or more devices need to be replaced, the reason should be documented in the patient's medical record, dispensing log, and Device Performance Issues Form. Additional devices are provided for this purpose. The unique serial numbers of the new components will be recorded in the patient's medical record, dispensing log, and the source documentation.

For device malfunction or complaints, complete the Device Performance Issues Log and submit to the Sponsor at Complaints@aerogenpharma.com within 48 hours. Failed devices will be set aside from the general supplies, inventoried and returned to the Sponsor or the Sponsor's designee.

5.5 Blinding

Clinical and research staff and Sponsor will be blinded to Active or Control dose assignments with the exception of the pharmacy staff and an unblinded Sponsor CRA. Should unblinding be necessary, the medical monitor for this study will work with the unblinded pharmacist or unblinded CRA to unblind the patient.

Active treatment (Flolan) is clear in color when reconstituted and Control treatment (0.9% sodium chloride solution) is also clear in color to maintain the study blind. The Control and Active treatments will be placed in identical 60 mL syringes and labelled in a blinded manner prior to leaving the pharmacy.

5.6 Prior and Concomitant Therapy

For patients who receive study drug, any medication (including over-the-counter [OTC] medications or other investigational therapies) or therapy administered to the patient during the course of the study (starting at Screening and 14 days prior) will be recorded on the Prior and Concomitant Therapy data collection forms. The Investigator will record any AE on the AE data collection forms for which a concomitant medication/therapy was administered.

5.6.1 Prohibited Concomitant Therapy

Other inhaled vasodilators.

5.7 Investigational Product (IP) Supplies and Accountability

Investigational product supplies will not be sent to the Investigator(s) until the following documentation has been received by the Sponsor:

- Written proof of approval of the protocol and its informed consent forms (ICFs) by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for the institution where the study is to be conducted. (Due to COVID-19 and the availability of the Active study medication, the study medication will be sent to the OSU pharmacy and held in quarantine until IRB approval and the completion of Study Initiation Visit (SIV), which may be conducted remotely or in person. A NTF will be sent to OSU pharmacy instructing that the study medication is not released for use until Sponsor notification.)
- An Investigator-signed and dated FDA Form 1572.
- A signed and dated curriculum vitae of the Principal Investigator including a copy of the Principal Investigator's current medical license (required in the US) or medical registration number on curriculum vitae.

The Investigator and study staff will be responsible for the accountability of all IP supplies (dispensing, inventory, and record keeping) following Aerogen Pharma instructions and adhere to Good Clinical Practice (GCP) guidelines as well as local and/or regional requirements.

Under no circumstances will the Investigator allow the IP to be used other than as directed by this protocol. IP will not be administered to any individual who is not enrolled into the study.

An accurate and timely record of the receipt of all IP; dispensing of IP to the patient; collection of unused IP; and subsequent return of unused IP to Aerogen Pharma must be maintained. This includes, but may not be limited to: (a) documentation of receipt of IP, (b) IP dispensing log, (c) IP accountability log, (d) all shipping service receipts, and (e) documentation of returned IP to the Sponsor. All forms will be provided by Aerogen Pharma. Any comparable forms that the investigational site wishes to use must be approved by Aerogen Pharma.

The supplies and inventory records must be made available, upon request, for inspection by the designated representative of Aerogen Pharma, a representative of the FDA, or a representative of a non-US health authority. All used and unused IP are to be returned to Aerogen Pharma at the conclusion of the study.

6. CRITERIA FOR EVALUATION

6.1 Primary Endpoint

1. Reduction of respiratory failure. Failure is defined by any one of the following:

    - Requires VV ECMO
    - Inability to extubate within 10 days or reintubation within < 24 hours
    - Change in S/F, oxygenation index and P/F ratio ($\geq$15%) from baseline to 12 hours, Days 1, 2, 3, 4, 5, 6, 7, 8, 9 and Day 10 (or end of treatment)

or

2. Reduction of cardiac or circulatory failure. Failure is defined by any one of the following:

    - Need to begin inotropic therapy or 10% increase in current vasopressor therapy
    - Worsening hemodynamic parameters
    - Cardiac troponin >20% from baseline
    - BNP $\geq$ 15% of baseline
    - Need for temporary mechanical circulatory support (IABP, Impella)
    - Requires VA ECMO

6.2 Secondary Endpoints

1. Improvement in oxygenation defined as any one of the following:
    - Stabilization of PaO2/FIO2 >250
    - Improvement in FIO2 by 50% or improvements $\geq$15% in S/F, P/F ratio from baseline at 12 hours, Day 5 and Day 10 (or end of treatment)
2. Improved clinical outcomes defined as one of more of the following:
    - Time to extubation following the site's extubation protocol

- Free from re-intubation
- Reduction in ICU days
- Reduction in the number of re-admissions to the ICU due to COVID-19 within 28 days
- Reduction in total hospital days
- Mortality [28 days] defined as Cardiopulmonary mortality or mortality from all causes

3. Safety and tolerability
    - Monitoring of adverse events (AEs), serious adverse events (SAEs), chest CT or Chest X-rays, vital signs, ventilatory/oxygenation parameters, and laboratory tests.

6.3 Exploratory endpoints will include (where available as part of standard of care):

- Change in LDH
- Change in fibrinogen
- Change in WBC count including lymphocytes and neutrophil subsets
- Change in triglycerides
- Change in ferritin
- Change in CRP / ESR
- Change in IL-6
- Change in D-Dimer

Changes in these parameters will be assessed for each patient from baseline to end of study as well as changes between the active and control groups.

6.4 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used and generally recognized as reliable, accurate, and relevant in studies of cardiac and respiratory function.

7. SAFETY ASSESSMENTS

Safety will be assessed through monitoring of adverse events (AEs) and serious adverse events (SAEs), laboratory tests, chest assessments (Chest CT or Chest X-ray), oxygenation/ventilatory parameters, and vital signs. Safety assessment frequency is shown in the Schedule of Assessments and Procedures.

7.1 General Safety Procedures

7.1.1 Vital Signs and Weight Measurements

Vital sign measurements, including systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) [beats per minute], respiratory rate (breaths per minute), and body temperature (in Celsius) will be obtained twice daily Days 1-10 or as clinically indicated. Weight (kg) will be obtained at the time of Screening and at Day 10 or end of VP treatment. Height will be obtained at the time of Screening. If unable to obtain height, the study staff will use the best reported historical height from patient or LAR.

7.1.2 Physical Examination

A physical examination will be conducted at the screening visit and may include assessments of general appearance; skin and lymphatics; eyes, ears, nose, throat; cardiovascular system; respiratory system; abdomen/gastrointestinal system; urological system; musculoskeletal and neurological systems. Other body systems may be examined as clinically indicated.

7.1.3 Laboratory Measurements

Clinical laboratory measurements to be performed are listed below. The Schedule of Assessments and Procedures shows the time points at which blood will be collected for clinical laboratory tests and pregnancy testing. The Baseline for laboratory tests is the Screening assessment.	
Category	Parameters
Hematology-CBC with diff	Hemoglobin, hematocrit, RBC, WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelets
Full Chemistry Panel	
Electrolytes	Sodium, potassium, chloride, bicarbonate, calcium
Liver function tests	AST, ALT, AP, total bilirubin
Renal function parameters	BUN, creatinine
Coagulation Studies	PT/PTT
Other	Serum or urine pregnancy test, COVID-19 diagnostic test, Troponin, and BNP (fibrinogen, ferritin, LDH, Triglycerides, D-Dimer, IL-6, ESR,CRP may be obtained if the patient's standard of care warrants the tests)

7.1.4 Chest Assessments

A Chest CT or Chest X-ray will be obtained at Screening and between days 3 to 8 as clinically indicated.

7.1.5 Time Prone Protocol

The time prone protocol is a standard of care in OSU's ICU. This will be in place for all days that patients are within the ICU.

7.2 Adverse Events

7.2.1 Definitions

Adverse events are any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship

with this treatment. For the purposes of this study, this will include unanticipated medical events in the judgment of the investigator. ***A pre-existing condition*** or symptom is one that is present at the start of the study and is reported as part of the patient's medical history. A pre-existing condition or symptom should be reported as an AE only if its frequency, intensity or character worsens during study treatment.

All AEs that occur from the time of the first dose of study medication through the End of Study (Day 28) will be recorded and reported as Treatment-Emergent Adverse Events (TEAE). All AEs must be appropriately documented in the patient's medical chart/source documentation and on the DCFs. When known, investigators should report syndromes rather than list symptoms associated with the syndrome.

All AEs that are ongoing at the conclusion of the study should be followed until: a) resolution/stable sequelae; b) the Investigator determines that it is no longer clinically significant; or, c) the study patient is lost to follow-up. If no follow-up is provided, the Investigator must provide a written justification.

7.2.2 Adverse Events of Special Interest (AESI)

Pulmonary edema and pulmonary hemorrhage are AEs of special interest due to the mode of action of epoprostenol. If an AE of special interest occurs, the Sponsor will be notified of this occurrence within 24 hours.

7.2.3 Grading of Adverse Events

The severity of each AE will be categorized using the following criteria:

- Grade 1 (Mild): usually transient; requires no special treatment and does not interfere with the patient's daily activities.
- Grade 2 (Moderate): produces a low level of inconvenience to the patient and may interfere with daily activities. These AEs are usually ameliorated by simple therapeutic measures.
- Grade 3 (Severe): interrupts daily activity and requires systemic drug therapy or other medical treatment.

7.2.4 Relationship to Study Medication/Study Device/Procedure

The Investigator must assess the relationship of each reported AE. The Investigator must make an assessment of the relationship of the AE to the study drug/study device/procedure using the following scale:

- Unrelated: The AE is definitely not or unlikely to be associated with study medication/study device/procedure and is judged due to causes other than the study medication/study device/procedure.
- Related: The AE is possibly or probably related with study medication/study device/procedure.

7.2.5 AE Outcomes

The following terms and definitions are used in assessing the final outcome of an AE:

- Recovered/Resolved - The patient has fully recovered, or by medical or surgical treatment, the condition has returned to the level observed at the first trial-related activity.
- Recovering/Resolving - The condition is improving and the patient is expected to recover from the event.
- Recovered/Resolved with sequelae - The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- Not recovered/Not resolved - The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known at the time of reporting.
- Fatal - This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as "recovered", "recovering", "recovered with sequelae" or "not recovered". An AE with fatal outcome must be reported as an SAE.

7.2.6 Laboratory Test and other Test Abnormalities as Adverse Events

A laboratory or other test (chest assessments, vital signs) abnormality should be reported as an AE if the Investigator considers the abnormality an AE or if the abnormality is associated with accompanying symptoms, requires medical/surgical intervention, leads to a change in study treatment, or results in discontinuation from the trial. When possible, syndromes not laboratory values, should be reported as AEs. For example, elevated hepatic transaminases associated with hepatitis should be reported as "hepatitis" and decreased hemoglobin and hematocrit requiring iron supplementation should be recorded as "anemia." Prior to reporting as an AE, abnormal tests should be repeated to verify the accuracy of the original result.

7.2.7 Serious Adverse Events

The Investigator is required to determine if each AE is a Serious Adverse Event (SAE). An SAE is any AE occurring after randomization and through Day 28 and results in any of the following outcomes:

- Death, or
- Is life-threatening, or
- Prolongation of existing hospitalization, or
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- Is a congenital anomaly/birth defect.

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

In the event of death, the cause of death should be recorded as the SAE (death is an outcome, not the AE itself).

Any planned procedures that require admission to hospital as well as any planned elective procedures (e.g., angioplasty) are not considered SAEs (unless the underlying condition has worsened or the procedure results in a worsening of the patient's condition). In addition, pregnancy that occurs during the course of the study or absence of a treatment effect will also not be considered to be an SAE and will be collected on a separate CRF.

7.2.8 Reporting for SAEs (24 Hours)

Regardless of causality, an SAE must be followed clinically until resolution or stabilization.

All SAEs after randomization and through Day 28 of the study must be reported to the Sponsor or the Sponsor's representative within 24 hours of the investigational site's knowledge of the occurrence. The investigational site will email a Serious Adverse Event Report (SAER) to the Sponsor and the Medical Monitor. Investigational sites will be provided with SAER forms. The Medical Monitor will work closely with the Sponsor to properly assess and report the SAE.

The SAE information emailed to the Sponsor or the Sponsor's representative will include the following (as available):

- Patient Number, Investigator name, and Site Number
- SAE information: event term, onset date, severity, and causal relationship
- Basic demographic information (e.g., age, gender, weight)
- The outcomes attributable to the event (death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, other important medical event[s])
- A summary of relevant test results, pertinent laboratory data, and any other relevant medical history
- The first and last dates of study drug administration.
- A statement whether study medication was discontinued or study medication administration schedule modified
- A statement whether event recurred after reintroduction of study medication if administration had been discontinued or withheld
- Supplemental anonymized information may include the following hospital records: laboratory results, radiology reports, progress notes, admission and emergency room notes, holding/observation notes, discharge summaries, autopsy reports, and death certificates

Supplemental information may be transmitted using a follow-up report and should not delay the initial report.

For regulatory purposes, initial reports of SAEs should be transmitted within the prescribed time frame as long as the following minimum information is available: patient number, suspect study medication, reporting source, and an event or outcome that can be identified as being both serious and unexpected for which the Investigator can make a relationship assessment.

7.3 Reporting of Pregnancy

Any pregnancy where the estimated date of conception occurs either prior to the End of Study must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment. The medical monitor may decide that unblinding of the patient treatment assignment may be necessary.

An induced abortion or a spontaneous abortion is considered to be an SAE and should be reported in the same timeframe and in the same format as all other SAEs.

Pregnancies must be reported as soon as possible but no later than one business day by email.

All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but not later than 24 hours of the investigational site's knowledge of the outcome.

8. PHARMACOKINETIC ASSESSMENTS

Not applicable.

9. SCHEDULE OF ASSESSMENTS AND PROCEDURES

The assessments and procedures for this study are described in detail below and presented in the Schedule of Assessments and Procedures located behind the Synopsis.

9.1 Study Evaluation Timepoints

9.1.1 Screening (within 14 days prior to Baseline Day 1)

Potential study patients will be recruited by the study staff from patients. The following assessments will occur prior to study enrollment:

- Informed consent (study procedures or assessments may be performed prior to consent as many screening study procedures were obtained as part of the patient's standard of care treatment).
- Demographic Information
- Medical History
- Physical Exam

- Prior Medication History
- Chest CT or Chest X-ray
- Inclusion/Exclusion Eligibility Assessment (including assessment of shortness of breath within the last 14 days)
- Serum/Urine Pregnancy Test (if woman of childbearing potential)
- Clinical Laboratory Sampling to include: Full Chemistry Panel including LFTs, CBC with Diff including neutrophils and lymphocytes, PT/PTT, troponin, and BNP (Triglycerides, LDH, ferritin, fibrinogen, CRP, ESR, IL 6 and D-Dimer may be collected if the subject's condition warrants it)
- COVID-19 diagnostic test such as molecular or antigen test (However the COVID test was obtained, documentation of the results must be available prior to study entry. For additional study COVID tests, whenever possible, please use the same type of test)
- Vital Signs
- Height & Weight (If height can't be obtained, use the best reported historical height)

9.1.2 Days 1-10 Treatment

9.1.2.1 Randomization

- Evaluate that the patient continues to be eligible for the study by assessing Inclusion/Exclusion Criteria.
- Once eligibility has been confirmed, a Subject number beginning with 101 and rising sequentially will be assigned to the next enrolled subject.
- A blinded order for the Investigational Drug Services group will be generated by EPIC for the next sequential subject to be randomized.
- The unblinded pharmacist will prepare the treatment assignment (Active or Control) for the next assigned Subject number.
- The reconstituted study drug will be protected from light and labelled in a blinded manner to ensure maintenance of the study blind.
- Subjects will be randomized to receive either Active or Control for a maximum of 10 days, as clinically indicated and at the discretion of the Investigator.

9.1.2.2 Baseline-Day 1 (0 Hour)

- Continue evaluation eligibility by assessing Inclusion/Exclusion Criteria.
- Study drug treatment will begin at a starting dose of 13.6 ng/kg/min based on the concentration used to calculate Active treatment in mL/hr and can be titrated up to 30.6 ng/kg/min or down to 3.4 ng/kg/min as clinically warranted. The B.Braun syringe pump will be set to the appropriate dose in mL/hr utilizing the subject's sex and height (ideal body weight).
- Vital signs will be assessed twice daily in AM and PM while on study drug. Efforts will be made to obtain vital signs at the same time each day. Vital signs include: temperature, pulse rate, respiration rate and blood pressure.
- Adverse Event/SAE assessment daily

- Concomitant medication evaluation daily
- Continuous pulse oximetry (SpO_2)
- Ventilatory parameters assessed twice daily while on study drug: Ventilator Type, Vent Mode, FiO_2, Inspiratory time, Mean Airway Pressure, Peak Inspiratory Pressure, Positive End Expiratory Pressure, Tidal Volume, and Respiratory Rate
- Time Prone Position-16 hours per day per OSU Protocol

9.1.2.3 Day 1-12 hours

- Continue to administer study drug if clinically indicated.
- Adverse Event/SAE assessment daily
- Concomitant medication evaluation daily
- Oxygenation measurement via continuous pulse oximetry (SpO_2)
- Ventilatory parameters assessed twice daily while on study drug: Ventilator Type, Vent Mode, FiO_2, Inspiratory time, Mean Airway Pressure, Peak Inspiratory Pressure, Positive End Expiratory Pressure, Tidal Volume, and Respiratory Rate
- Vital signs will be assessed twice daily in AM and PM. Efforts will be made to obtain vital signs at the same time each day. Vital signs include: temperature, pulse rate, and blood pressure.
- Time Prone Position-16 hours per day per OSU Protocol

9.1.2.4 Days 2-10 (While on study drug)

- Continue to administer study drug if clinically indicated.
- Adverse Event/SAE assessment daily
- Concomitant medication evaluation daily
- Oxygenation measurement via continuous pulse oximetry (SpO_2)
- Ventilatory parameters assessed twice daily: Ventilator Type, Vent Mode, FiO_2, Inspiratory time, Mean Airway Pressure, Peak Inspiratory Pressure, Positive End Expiratory Pressure, Tidal Volume, and Respiratory Rate
- Vital signs will be assessed twice daily in AM and PM. Efforts will be made to obtain vital signs at the same time each day. Vital signs include: temperature, pulse rate, and blood pressure.
- Time Prone Position-16 hours per day per OSU Protocol

- Chest X-ray (Days 3-8 as clinically indicated)
- Full Chemistry Panel including LFTs, CBC with Diff including neutrophils and lymphocytes, PT/PTT, troponin, and BNP(Days 5 & 10).
- Triglycerides, LDH, ferritin, fibrinogen, CRP, ESR, IL 6 and D-Dimer may be collected if the subject's condition warrants it at Days 5 and Day 10.
- Obtain weight. (Day 10 only or at end of study drug dosing)

9.1.2.5 Weaning

See Section 5.3.4 and Table 3 for weaning guidelines.

9.1.3 Day 28/End of Study (EOS)

- Assess AEs/SAEs
- Assess Mortality
- Assess concomitant medications

9.2 Data Collection

Investigator or designee will enter the information required by the protocol onto source documents and enter data into data collection forms (DCFs) in an excel spreadsheet provided by Aerogen Pharma.

9.3 Clinical Data Management

Data from source documents will be verified against the DCF and any discrepancies will be clarified and resolved with study staff.

9.4 Database Quality Assurance

All data will be remotely monitored by the Sponsor due to the COVID-19 pandemic. Should restrictions be lifted at OSU, an on-site visit may occur if all parties are in agreement.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Methods

A Statistical Analysis Plan will be not be developed as this is an exploratory trial. Any statistical evaluation will be handled internally by Aerogen Pharma or their designee.

10.2 Determination of Sample Size

The number of patients has been selected to enable an adequate clinical assessment of pharmacodynamics, safety, and tolerability parameters without presenting undue risk to a large number of patient's being exposed to this investigational product.

10.3 Analyses Sets

All patients who are enrolled in the study and who receive at least one dose of study drug will be included in the intent-to-treat (ITT) analyses of pharmacodynamic and safety data. All available data will be used and missing data will not be estimated or carried forward in any statistical summary or analyses.

Descriptive summary statistics include the number of patients, mean, median, percent coefficient of variation (% CV) (if required), standard deviation, and minimum and maximum values (quantitative variables) or the number of patients and percentages by category (qualitative variables). Changes will be assessed as the difference between baseline measurements and the appropriate post-dose measurements unless otherwise specified. Mean differences between active and control groups (when available) will be assessed and significance will be determined on the basis of a 95% CI. Individual patient listings of data will also be provided to allow for review of all pharmacodynamic, safety, and tolerability parameters.

10.4 Randomization

Patients will be randomized 1:1. A randomization schedule will be provided to the unblinded pharmacist. Should unblinding be requested due to a medical emergency, the unblinded pharmacist will work with the medical monitor or Sponsor unblinded CRA to obtain the required information.

10.5 Demographic and Other Baseline Characteristics

Continuous demographic and other baseline characteristics (such as age, weight, and height) will be summarized using n, mean, SD, median, minimum, and maximum. Qualitative characteristics (such as gender and race) will be summarized by counts and percentages.

10.6 Criteria for Evaluation

10.6.1 Primary Efficacy Endpoint

The primary efficacy endpoint:

1. Reduction of respiratory failure. Failure is defined by any one of the following:

    - Requires VV ECMO
    - Inability to extubate patient within 10 days or reintubation within <24 hours
    - Change in S/F, oxygenation index and P/F ratio (≥15%) from baseline to 12 hours, Days 1, 2, 3, 4, 5, 6, 7, 8, 9 and Day 10 (or end of treatment)

or

2. Reduction of cardiac or circulatory failure. Failure is defined by any one of the following:

    - Need to begin inotropic therapy or 10% increase in current vasopressor therapy

- Worsening hemodynamic parameters
- Cardiac troponin >20 % from baseline
- BNP ≥ 15% of baseline
- Need for temporary mechanical circulatory support (IABP, Impella)
- Requires VA ECMO

10.6.2 Secondary Efficacy Endpoints

Key secondary endpoints include:

1. Improvement in oxygenation defined as any one of the following:
   - Stabilization of PaO2/FIO2 >250
   - Improvement in FIO2 by 50% or improvements ≥15% in S/F, P/F ratio from baseline at 12 hours, Day 5 and Day 10 (or end of treatment)
2. Improved clinical outcomes defined as one of more of the following:
   - Time to extubation following the site's extubation protocol
   - Free from reintubation
   - Reduction in ICU days
   - Reduction in the number of re-admissions to the ICU due to COVID-19 within 28 days
   - Reduction in total hospital days
   - Mortality [28 days] defined as Cardiopulmonary mortality or mortality from all causes
3. Safety
   - Monitoring of adverse events (AEs), serious adverse events (SAEs), chest CT or Chest X-rays, vital signs, ventilatory/oxygenation parameters, and laboratory tests.

10.6.3 Key Exploratory Endpoints include:

- Change in LDH
- Change in fibrinogen
- Change in WBC count including lymphocytes and neutrophil subsets
- Change in triglycerides
- Change in ferritin
- Change in CRP / ESR
- Change in IL-6
- Change in D-Dimer

Changes in these parameters will be assessed for each patient from baseline to end of study as well as changes between the active and control groups.

10.7 Extent of Exposure

Exposure data will be summarized by using frequencies and percentages.

10.8 Safety Analyses

Safety measurements include AE/SAEs, vital signs, chest assessments (Chest CT or Chest X-ray), laboratory tests, and oxygenation/ventilatory parameters. Safety data will be summarized by using frequencies and incidence rates.

10.8.1 Adverse Events

AEs will be classified into standardized medical terminology from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be presented by preferred term nested within System Organ Class. Verbatim description and all MedDRA level terms, including the lower level terms, for all AEs will be contained in the data listings of the clinical study report (CSR).

AEs will be summarized by presenting the incidence of AEs. Although a MedDRA term may be reported more than once for a patient, that patient will be counted only one time in the incidence count for that MedDRA term.

Treatment-emergent adverse events (TEAEs) will be analyzed. AEs that are not treatment-emergent will be listed. A TEAE is defined as

- AEs that emerge during treatment, having been absent at pretreatment, or
- Reemerge during treatment, having been present at pretreatment but stopped prior to treatment, or
- Worsen in severity or frequency during treatment relative to the pretreatment state, when the AE is continuous.

Adverse events of special interest (AESI) will be analyzed. An AESI is defined as:

- Serious or non-serious adverse that is one of scientific and medical concern specific to the sponsor's product for which ongoing monitoring and rapid communication by the investigator to the sponsor is required
- Events or symptoms thought to potentially be associated with the investigational compound, device, or disease under study, or
- Can arise with any use of a drug/device (e.g. off-label use, use in combination with another approved drug), with any route of administration, formulation, or dose, including an overdose.

10.8.2 Laboratory Values

Clinical laboratory results post-Baseline will be evaluated for markedly abnormal values. For the incidence of markedly abnormal laboratory values, each patient may be counted once in the laboratory parameter value high and in the laboratory parameter low

categories as applicable. Descriptive summary statistics (e.g. mean, SD, median, minimum, maximum) for laboratory values and changes from baseline will be evaluated.

10.8.3 Vital Signs

Vital sign values will be evaluated on an individual basis by patient. Abnormal vital sign values will be identified as those outside (above or below) the reference range. Descriptive summary statistics (e.g., mean, SD, median, minimum, maximum) for vital sign parameters and changes from Baseline will be evaluated.

10.9 The Procedure for Revising the Statistical Analysis Plan

Not Applicable.

11. ADMINISTRATIVE PROCEDURES AND INSTRUCTIONS

11.1 Ethics

11.1.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an IRB or IEC constituted and functioning in accordance with International Conference on Harmonization (ICH) E6, Section 3, and any local regulations, i.e., Federal Regulations, Title 21 Code of Federal Regulations (CFR) Part 56. Any protocol amendment and/or revision to the ICF will be resubmitted to the IRB/IEC for review and approval (except for changes involving only logistical or administrative aspects of the study (e.g., change in CRA[s], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

A signed letter of study approval from the IRB/IEC Chairman must be sent to the Principal Investigator with a copy to the Sponsor prior to study start. If the IRB/IEC decides to suspend or terminate the study, the Investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the Sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the Investigator or Sponsor, depending on local regulatory obligations. If the Investigator is required to report to the IRB/IEC, he/she will forward a copy to the Sponsor at the time of each periodic report. The Investigator or the Sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable AEs per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the Investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

11.1.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating practices of Aerogen Pharma (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- ICH - E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonization of Pharmaceuticals for Human Use.
- US CFR dealing with clinical studies (21 CFR, including parts 50 and 56 concerning Informed Patient Consent and IRB regulations).

11.1.3 Patient Information and Informed Consent

As part of administering the informed consent document, the Investigator must explain to each patient or their legally authorized representative (LAR), the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, and currently available alternative treatments. Each patient must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The patient or their LAR should understand the statement before signing and dating it and will be given a copy of the signed document. The patient or their LAR will be asked to sign an informed consent prior to any study-specific procedures being performed (except for study procedures that were conducted as a part of the patient's standard of care). No patient can enter the study before his/her informed consent has been obtained. Due to the COVID-19 pandemic and restrictions on hospital visitors, informed consent may be obtained via telephone or video conference call if the patient is incapacitated or sedated due to the severity of their illness. A witness for the study team should be present when a call or video conference is occurring with the patient's LAR. This process should be carefully documented in the subject's medical records.

An unsigned copy of an IRB/IEC and Sponsor-approved written informed consent must be prepared in accordance with ICH E 6, Section 4, and all applicable local regulations, i.e., Federal Regulations, Title 21, CFR Part 50, and provided to the Sponsor. Each patient or their LAR must sign (or give verbal consent with study staff witnessing the verbal consent) an approved informed consent prior to study participation. The form must be signed and dated by the appropriate parties. The original signed ICF for each patient will be verified by the Sponsor and kept in the study center's investigational site files.

The patient should be informed in a timely manner if new information becomes available that might be relevant to the patient's willingness to continue participation in the trial. The communication of this information should be documented.

11.2 Administrative Procedures

11.2.1 Changes to the Protocol

There are to be no changes to the protocol without written approval from the Sponsor. Protocols will be followed as written.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of patients, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRBs/IECs of all investigational sites and, as required, by the regulatory authority. These requirements should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all patients included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary for safety reasons, the Medical Monitor must be notified promptly and the IRB/IEC for the site must be informed as soon as possible.

Changes affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval, but the IRB/IEC must be kept informed of such changes. In these cases, the Sponsor will send a letter to the site for forwarding on to the IRB/IEC detailing such changes.

11.2.2 Adherence to the Protocol

The Investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.2.3 Monitoring Procedures

The Sponsor or Sponsor's representative will maintain contact with the Investigator and designated staff by telephone, letter, and/or email between study visits. Monitoring visits to each investigational site will be conducted by the sponsor either remotely or in person.

In accordance with ICH E6, Section 6.10, source documents include, but are not limited to the following:

- Clinic, office, hospital charts.
- Copies or transcribed health care provider notes which have been certified for accuracy after production.
- Recorded data from automated instruments such as mechanical ventilators, x-rays, and other imaging reports, e.g., sonograms, computed tomography scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, electroencephalographs, polysomnography, pulmonary function tests (regardless of how these images are stored, including microfiche and photographic negatives).
- Records of telephone contacts.
- Diaries or evaluation checklists.
- Investigational product distribution and accountability logs maintained in pharmacies or by research personnel.
- Laboratory results and other laboratory test outputs, e.g., serum pregnancy test result documentation.
- Correspondence regarding a study patient's treatment between physicians or memoranda sent to the IRBs/IECs.

- CRF components (e.g., questionnaires) that are completed directly by patients and serve as their own source.

11.2.4 Recording of Data

In order to provide the Sponsor with accurate, complete, and legible records following criteria are to be maintained. The Investigator will enter the information required by the protocol onto the data collection forms (DCFs) provided by the sponsor as agreed upon with the research staff.

11.2.5 Data Storage and Retention of Records

The circumstances of completion or termination of the study notwithstanding, the Investigator has the responsibility to retain all study documents, including but not limited to the protocol, copies of data collection forms (DCFs) , Investigator's Brochure, regulatory agency registration documents, e.g., FDA 1572 form, ICFs, and IRB/IEC correspondence. The investigational site should plan on retaining study documents as follows:

- For at least two years following the date a marketing application is approved for the investigational product for the indication for which it is being investigated, or

- Until two years after the investigation is formally discontinued and no application is to be filed or if the application is not approved.

It is requested that at the completion of the required retention period, or should the Investigator retire or relocate, the Investigator contacts the Sponsor, allowing the Sponsor the option of permanently retaining the study records.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Data will be coded (de-identified), stored in a secure electronic database during and after the study, and will not be shared with unauthorized persons. The principal investigator and co-investigator will have access to the data to review and analyze the data, as described in this protocol. For the protection and privacy of the patients, no identifying information will be released. Data will be retained and possibly used in the future for further analysis. All identifiers will be removed and not be shared at any time.

11.2.6 Handling of Investigational Product

Investigational study drug (Flolan) will be inventoried and maintained within the site's Investigational Drug Services . It will be stored according to their protocols and procedures. The study drug should not be dispensed to patients in the VentaProst COVID trial (APC-VPCOV-CLN-001) until a favorable IRB approval has been obtained by the OSU IRB and a study initiation visit has been conducted by the Sponsor. Investigational device supplies must be kept in an appropriate secure area (e.g., locked cabinet) and stored according to the conditions specified on the investigational product labels. The Investigator (or designated pharmacist) must maintain an accurate record of the shipment and dispensing of the IP (both device and drug) in an IP accountability log, a copy of which must be given to the Sponsor at the end of the study. An accurate record

of the date and amount of IP dispensed to each patient must be available for inspection at any time. The assigned sponsor representative will review these documents along with all other study conduct documents at an appropriate interval of visit to the investigational site once IP has been received by the investigational site. Due to COVID-19 a physical inventory of IP (drug and device supplies) may not be possible. If at all possible, an inventory of supplies should be conducted via video conferencing. If video conferencing is not possible, study staff will inventory supplies and provide documentation to Aerogen Pharma.

All IP supplies (with the exception of OSU stock 0.9% sodium chloride solution supplies) are to be used only for this protocol and not for any other purpose. The Investigator (or designated pharmacist) must not destroy any IP product labels or any partly used or unused IP supply without Sponsor authorization. At the conclusion of the study and as appropriate during the course of the study, the Investigator (or designated pharmacist) will return or properly dispose of all used IP. Unused investigational device and drug components will be returned to Aerogen Pharma at the conclusion of the study.

11.2.7 Publication of Results

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each Investigator and Aerogen Pharma, as appropriate.

11.2.8 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the course of this study will be kept confidential by the Investigator, the Investigator's staff, and IRB/IEC and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study without the written consent of the Sponsor. No data collected as part of this study will be utilized in any written work, including publications, without the written consent of Sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in the Confidentiality Agreement between the Sponsor and the Investigator. All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Confidentiality Agreement between the Investigator and Sponsor (provided by the Sponsor).

11.2.9 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time.

The Investigator reserves the right to discontinue the study should his/her judgment so dictate. If the Investigator terminates or suspends a trial without prior agreement of the Sponsor, the Investigator should inform the Institution where applicable, and the Investigator/Institution should promptly inform the Sponsor and the IRB/IEC and should provide the Sponsor and the IRB/IEC a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.2.10 Patient Insurance and Indemnity

The Sponsor will provide the insurance in accordance with local guidelines and requirements as a minimum for the patients participating in this study.

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