PROTOCOL TITLE	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
PROTOCOL NUMBER	APC-VP-CLN-001
INVESTIGATIONAL PRODUCT	VentaProst
INDICATION	Pulmonary Vascular Resistance in Cardiac Surgery Patients
PHASE	Phase 2a
SPONSOR	Aerogen Pharma Limited 1660 S Amphlett Boulevard, Suite 360 San Mateo, CA 94402 United States
MEDICAL MONITOR	Pia Mikkelsen Lynch, MD Aerogen Pharma Mobile Telephone: +1 404 963 9090 (US) /+45 5381 2607 (DK) Facsimile: +1-678-828-5549 Email: plynch@pmlmedical.com
APPROVAL DATE	28 November 2017
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.

PROTOCOL APPROVAL PAGE

PROTOCOL TITLE 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

PROTOCOL NUMBER APC-VP-CLN-001

APPROVAL DATE 28 November 2017

28 NOV 2017
Date

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INVESTIGATOR'S SIGNATURE PAGE

PROTOCOL TITLE: 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

PROTOCOL NUMBER: APC-VP-CLN-001

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-VP-CLN-001
Title of Study	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
Study Centers	Approximately three clinical sites in the US
Phase	Phase 2a
Objectives	**Primary Objective** • To identify the relative dose equivalency between effective conventionally administered aerosolized Veletri® and VentaProst doses **Secondary Objectives** • To evaluate the safety and tolerability of VentaProst doses in a patient population post cardiac surgery with cardiopulmonary bypass (CPB) • To demonstrate that VentaProst dose titration to achieve at least a 15% improvement in one or more hemodynamic parameters (as defined by the clinical team) is safe and effective • To demonstrate the pharmacodynamic (PD) equivalence (based on cardiovascular parameters, indices of oxygenation, and ventilator support) of VentaProst doses to aerosolized Veletri doses • To identify cardiovascular medications administered concomitantly with VentaProst • To monitor ventilator support needed
Study Design	**Part I (see Appendix 1 for Study Design Schematic)** The first part of this study will be conducted in approximately 10 consented post-operative cardiothoracic surgery patients on cardiopulmonary bypass (CPB) who are receiving aerosolized Veletri (in accordance with each site's standard of care guidelines) and who demonstrate at least a 15% improvement in one or more hemodynamic parameters (as defined by the clinical team) when treated with aerosolized Veletri. This part of the study is designed to demonstrate the dose equivalence between aerosolized Veletri and VentaProst using a patient's hemodynamic parameters, with the goal to determine the VentaProst dose necessary to achieve a hemodynamic response that is not less than 90% of the effect observed with 50 ng/kg/min aerosolized Veletri. Arterial oxygen saturation (SaO_2) must be maintained at or above the level obtained with aerosolized Veletri administration. Qualifying patients will: • Receive aerosolized Veletri 50 ng/kg/min in the OR/ICU • Have hemodynamic parameters measured before and after aerosolized Veletri administration to determine changes o *IF AT LEAST A 15% IMPROVEMENT IN ONE OR MORE HEMODYNAMIC PARAMETERS (AS DEFINED BY THE CLINICAL TEAM) IS SEEN WITH AEROSOLIZED VELETRI AFTER STABILIZATION IN THE ICU*:

- Be administered VentaProst as follows: Setup VentaProst inline to the ventilator circuit, start nebulization, then stop conventional Veletri pump flow and nebulizer while still inline. Do not remove Veletri administration system until VentaProst administration is confirmed

- *IF LESS THAN A 15% IMPROVEMENT IN ONE OR MORE HEMODYNAMIC PARAMETERS (AS DEFINED BY THE CLINICAL TEAM) IS SEEN WITH AEROSOLIZED VELETRI AFTER STABLIZATION IN THE ICU*:
  - Not be administered VentaProst

- Receive a calculated equivalent starting dose of 17 ng/kg/min of VentaProst while still on mechanical ventilation
- Receive increases in the VentaProst dose in 20% increments (refer to the VentaProst Pharmacy Manual) every 15 minutes until at least 90% of the hemodynamic effect observed with 50 ng/kg/min aerosolized Veletri is achieved while still on mechanical ventilation

Once a VentaProst dose equivalence has been achieved, patients will be weaned from VentaProst. VentaProst weaning will occur from mechanical ventilation only. If the patient has been extubated and is on institution's standard of care delivery system for administering aerosolized Veletri, weaning will occur in accordance with each site's standard of care guidelines for weaning of aerosolized Veletri. The table below shows the typical weaning steps for aerosolized Veletri from mechanical ventilation. If weaning from VentaProst occurs while on mechanical ventilation, doses will be decreased in 20% increments of the VentaProst equivalent dose.

Weaning Guideline

Aerosolized Veletri (from Ventilator)	VentaProst (from Ventilator)
50 ng/kg/min	Dose Equivalence to aerosolized Veletri 50 ng/kg/min
40 ng/kg/min	80% of Dose Equivalence
30 ng/kg/min	60% of Dose Equivalence
20 ng/kg/min	40% of Dose Equivalence
10 ng/kg/min	20% of Dose Equivalence

Patients on mechanical ventilation 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 increments of 20% of the VentaProst equivalent dose, with a minimum of 30 minutes between changes, down to 20% of the dose before discontinuation. 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 (changes in combined hemodynamic parameters) or a decrease in oxygenation indicated by either arterial or central blood oxygenation saturation 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. Final hemodynamic measurements will be collected 15 to 30 minutes after discontinuation of VentaProst.

Patients will be monitored for safety and PD efficacy throughout the initial aerosolized Veletri and VentaProst administrations.

Part II (see Appendix 2 for Study Design Schematic)

The second part of the study will be conducted in approximately 10 consented cardiothoracic surgical patients requiring CPB with perioperative pulmonary hypertension (pulmonary arterial mean pressure [mPAP] ≥ 25 mm Hg). This part of the study is designed to establish a dose response relationship of VentaProst to PD effect by dose escalation in these patients. The goal will be to determine the VentaProst dose necessary to achieve at least a 15% improvement in one or more hemodynamic parameters (as defined by the clinical team).

Hemodynamic measurements will be taken prior to cardiac surgery (after induction) with CPB, prior to dosing with VentaProst, and after each dose titration step.

Qualifying patients will:

- Receive a starting dose of 3.4 ng/kg/min of VentaProst
- Have hemodynamic parameters monitored and recorded
- Receive increase in the VentaProst dose in 3.4 ng/kg/min increments (refer to VentaProst Pharmacy Manual)
    - *IF GREATER THAN A 15% IMPROVEMENT IN ONE OR MORE HEMODYNAMIC PARAMETERS (AS DEFINED BY THE CLINICAL TEAM) IS SEEN WITH THE INITIAL VENTAPROST DOSE*, but *NO* additional clinically meaningful change is seen with this first dose escalation:
        - Have the VentaProst dose reduced to the initial dose level
    - *IF GREATER THAN A 15% IMPROVEMENT IN ONE OR MORE HEMODYNAMIC PARAMETERS (AS DEFINED BY THE CLINICAL TEAM) IS SEEN WITH THE INITIAL VENTAPROST DOSE*, but *AN* additional clinically meaningful change is seen with the first dose escalation:
        - Continue to receive VentaProst in increasing steps of 3.4 ng/kg/min every 5 to 15 minutes as clinically indicated until no further improvements in one or more hemodynamic parameters are achieved or until dose-limiting pharmacological effects are elicited or a tolerance limit to VentaProst is established.
    - *IF LESS THAN A 15% IMPROVEMENT IN ONE OR MORE HEMODYNAMIC PARAMETERS (AS DEFINED BY THE CLINICAL TEAM) IS SEEN WITH FIRST DOSE INCREASE*:
        - Continue to receive VentaProst in increasing steps of 3.4 ng/kg/min every 5 to 15 minutes as clinically indicated until no further improvements in one or more hemodynamic parameters are achieved or until dose-limiting pharmacological effects are elicited or a tolerance limit to VentaProst is established.
        - Have the VentaProst dose reduced to the previous dose level (after the VentaProst dose has stabilized) at which one or more hemodynamic parameter showed maximum improvement. The VentaProst dose level will remain at this setting until clinical conditions determine the need for changing the dose.

Arterial and central venous blood oxygenation parameters will also be considered in the titration process.

Patients requiring post-operative support with epoprostenol will be allowed to continue on VentaProst treatment in the ICU as long as they are still on mechanical ventilation. For weaning, doses will be decreased in increments of 20% of the VentaProst equivalent dose, with a minimum of 30 minutes between changes, down to 20% of the dose before discontinuation (see Weaning Guideline from Part I above).

	VentaProst weaning will occur from mechanical ventilation only. If the patient is extubated and placed on institution's standard of care delivery system for administering aerosolized Veletri, weaning from aerosolized Veletri will follow each institution's guideline. Hemodynamic, oxygenation, and ventilator parameters will be obtained before and at 15 to 30 minutes after each VentaProst dose change to demonstrate the effect of the changes. Final measurements will be collected 15 to 30 minutes after discontinuation of VentaProst.
Number/Type of Patients	Approximately 10 patients will be enrolled in each part of this study. A minimum of three patients at an individual site will be enrolled in Part I of the study before the site can continue to Part II.
Inclusion Criteria	Patients are eligible for this study if they meet all of the following criteria: 1. Women and Men 18 to 80 years of age 2. Provide written informed consent 3. Willing and able to comply with all aspects of the protocol 4. For patients in Part I: a. Undergo cardiac surgery on CPB (including planned cardiac transplantation) b. Clinically require treatment with and receive aerosolized Veletri c. Demonstrate a clinically meaningful hemodynamic response to aerosolized Veletri (defined as at least a 15% improvement in one or more hemodynamic parameters [as defined by the clinical team]) 5. For patients in Part II: a. Undergo cardiac surgery with CPB (including planned cardiac transplantation) b. Have perioperative pulmonary hypertension (mPAP $\geq$ 25 mm Hg) c. Clinically require treatment with inhaled epoprostenol
Exclusion Criteria	Patients are **NOT** eligible for this study if they meet any of the following criteria: 1. Current smoker (i.e., within the last 30 days) 2. Emergency operative status 3. Upper and/or lower respiratory tract infection within four weeks of screening 4. Contraindication to transesophageal echocardiogram (TEE) including esophageal disease or unstable cervical spine 5. Renal (creatinine > 2.0 mg/dL) or severe hepatic impairment 6. Thromboembolic disease treated with anticoagulant therapy 7. Bleeding disorders 8. Presence or history of significant restrictive or obstructive lung disease (FEV_1 and/or FVC < 60% of predicted normal lung function) 9. History of concurrent malignancy or recurrence of malignancy within two years prior to Screening (not including patients with < 3 excised basal or squamous cell carcinomas) 10. History of a diagnosis of drug or alcohol dependency or abuse within one year 11. Recent history of stroke or transient ischemic attack (within six months prior to Screening) not due to trauma, repaired vascular malformation, or aneurysm 12. Significantly abnormal laboratory tests at Screening, including: a. Alkaline phosphatase (AP), alanine aminotransferase (ALT, SGPT), aspartate aminotransferase (AST, SGOT), or total bilirubin >2.5X of the upper limit of normal (ULN)

	b. Hemoglobin < 9 gm/dL, white blood count (WBC) count < 2500 mm^3, neutrophil count < 1500 mm^3, platelet count < 100×10^3/ mm^3 c. Evidence of hemoglobinopathy (including but not limited to sickle cell disease, thalassemia, hemoglobin M and variants with high oxygen affinity). 13. Pregnant or breastfeeding 14. Treatment with an investigational drug, biologic, or investigational cardiac implant within 30 days preceding the first dose of study medication or plans to take another investigational drug or biologic within 30 days of study completion 15. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with trial participation or investigational product administration or may interfere with the interpretation of trial results and, in the judgment of the Investigator or Sponsor, would make the patient inappropriate for entry into this trial 16. Any condition where aerosolized epoprostenol is contraindicated 17. Known allergy or sensitivity to epoprostenol, any of its ingredients, or the diluent (glycine)
Study Treatment(s)	**Part I** Study treatments are: • Aerosolized Veletri 50 ng/kg/min administered in accordance with each site's standard of care guidelines • VentaProst Patients who demonstrate at least a 15% improvement in one or more hemodynamic parameters (as defined by the clinical team) with aerosolized Veletri will be crossed over to a calculated VentaProst equivalent dose of 17 ng/kg/min with subsequent dose titration increases of 20% increments (refer to VentaProst Pharmacy Manual) every 15 minutes until a hemodynamic response that is not less than 90% of the effect observed with 50 ng/kg/min aerosolized Veletri is achieved. **Part II** Study treatment is VentaProst at a starting dose of 3.4 ng/kg/min of VentaProst, followed by 3.4 ng/kg/min dose titration increases (refer to VentaProst Pharmacy Manual) every 5 to 15 minutes as clinically indicated until no further improvements in one or more hemodynamic parameters are achieved. VentaProst doses will be decreased to the prior level once a dose response plateau is observed.
Duration of Treatment	**Part I** Individual patient participation is expected to be approximately **5** weeks including Screening, Intra-Operative, Aerosolized Veletri Treatment, VentaProst Treatment, and End of Study. The duration of study participation for each patient is as follows: • Screening: up to 30 days • Intra-Operative: 3 – 8 hours • Aerosolized Veletri Treatment administered in accordance with each site's standard of care guidelines (OR/ICU): 24+ hours (dependent on multiple factors) • VentaProst Treatment (ICU): 24+ hours (dependent on multiple factors) • End of Study: 4+ hours (dependent on multiple factors) **Part II** Individual patient participation is expected to be approximately **5** weeks including Screening, Intra-Operative, VentaProst Treatment (OR/ICU), and End of Study. The duration of study participation for each patient is as follows:

	• Screening: up to 30 days • Intra-Operative: 3 – 8 hours • VentaProst Treatment (OR/ICU): 24+ hours (dependent on multiple factors) • End of Study: 4+ hours (dependent on multiple factors)

Criteria for Evaluation	Primary Endpoint
	Determination of the equivalent dose of VentaProst necessary to achieve a hemodynamic response that is not less than 90% of the effect observed with 50 ng/kg/min aerosolized Veletri
	Secondary Endpoints
	• Safety of VentaProst dosing regimen
	  o Monitoring of adverse events (AEs), physical examinations, laboratory tests, and electrocardiograms
	• Effect of VentaProst dosing regimen on:
	  o Cardiovascular Parameters
	  ▪ Pulmonary Vascular Resistance (PVR)
	  ▪ Pulmonary Arterial Pressure (PAP)
	  ▪ Systemic Arterial Pressure
	  ▪ Central Venous Pressure (CVP)
	  ▪ Pulmonary Capillary Wedge Pressure (PCWP)
	  ▪ Cardiac Output (CO)
	  o Oxygenation
	  ▪ Arterial Oxygen Saturation (SaO_2) or Oxygen Saturation by Pulse Oximetry (SpO_2)
	  ▪ Partial Pressure of Oxygen in Arterial Blood (PaO_2)
	  o Ventilator Support
	  ▪ Fraction of Inspired Oxygen (FiO_2)
	  ▪ Ventilator pressures
	  ▪ Ventilator volumes
	  ▪ Duration of intubation
	• Number and type of cardiovascular medications required through end of study

Criteria for Conversion to Conventional Therapy	At any time during VentaProst administration, patients will be crossed over to standard therapy of aerosolized Veletri if they meet one or more of the following pre-defined criteria for a deterioration in their condition: • Severe postoperative mediastinal bleeding (> 500 mL/hr) • Hemoptysis • If a clinically inadequate response to VentaProst is observed, the patient may be converted back to aerosolized Veletri administered in accordance with each site's standard of care guidelines at the investigator's discretion Additionally, patients will be crossed over to standard of care therapy with aerosolized Veletri after extubation.
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. Individual patient listings of data will also be provided to allow for review of all

	pharmacodynamic, safety, and tolerability parameters. The number of patients has been selected to enable an adequate clinical assessment of pharmacodynamic, safety, and tolerability parameters without presenting undue risk to a large number of patient's exposure to this investigational product. Further details will be included in the Statistical Analysis Plan.
Efficacy Analysis	Efficacy will be secondarily determined by summarizing success or failure to meet the pharmacodynamics goals of the study.
Safety Analyses	Safety data will be summarized using frequencies and incidence rates.

Table 1 – Schedule of Assessments and Procedures – Part I

Study Procedures	Screening	Intra-Operative	Aerosolized Veletri Treatment Period (OR/ICU)	VentaProst Treatment Period (ICU)	End of Study
Written Informed Consent	X				
Demographics	X				
Assign Patient ID	X				
Medical History	X				
Medication History	X				
Physical Examination	X				X
Vital Signs/Weight/Height	X				X[12]
12-Lead ECG	X				X
Spirometry	X[11]				
Clinical Laboratory Sampling	X				X
Serum Pregnancy Test	X				X
Inclusion/Exclusion Criteria	X	X			
Cardiac Surgery with CPB		X			
Administer Aerosolized Veletri			X[6]		
Administer VentaProst				X[9]	
Hemodynamic Parameters[1]		X[5]	X[7,8]	X[10]	
Oxygenation Measurements[2]			X[7]	X[10]	
Ventilator Parameters[3]			X[7]	X[10]	
AE Monitoring[4]		X			X
Concomitant Medications	X	X			X

[1] Hemodynamic parameters include, but not limited to, Cardiac Index (CI), Cardiac Output (CO), Central Venous Pressure (CVP), Diastolic Pulmonary Arterial Pressure (dPAP), Diastolic Systemic Arterial Pressure (dSAP), Heart Rate (HR), Mean Pulmonary Arterial Pressure (mPAP), Mean Systemic Arterial Pressure(mSAP), Pulmonary Capillary Wedge Pressure (PCWP), Pulmonary Vascular Resistance (PVR), Rhythm, Systolic Pulmonary Arterial Pressure (sPAP), and Systolic Systemic Arterial Pressure (sSAP)

[2] Oxygenation measurements include SaO_2 or SpO_2 and PaO_2

[3] Ventilator parameters include Ventilator Type, Ventilator Mode, FiO_2, Inspiratory Time, Mean Airway Pressure, Peak Inspiratory Pressure, Positive End Expiratory Pressure, and Respiratory Rate

[4] To include unanticipated medical events in the judgment of the investigator

[5] Measure hemodynamic parameters prior to cardiac surgery with CPB and prior to dosing with aerosolized Veletri

[6] Initiate aerosolized Veletri dose at 50 ng/kg/min in accordance with each site's standard of care guidelines and stabilize the patient on aerosolized Veletri for at least 15 minutes

[7] Measure hemodynamic, oxygenation, and ventilator parameters after stabilization of aerosolized Veletri

[8] Determination of hemodynamic response from baseline for study inclusion, study continuation, and transition to VentaProst

[9] Initiate VentaProst dose at the calculated equivalent dose of 17 ng/kg/min; titrate up in 20% increments every 15 minutes (refer to VentaProst Pharmacy Manual); continue until dose is achieved that matches the hemodynamic measurements obtained with aerosolized Veletri dosing; stabilize patient on VentaProst for at least 15 minutes

[10] Measure hemodynamic, oxygenation, and ventilator parameters before and at 15 to 30 minutes after each VentaProst dose (during dosing, stabilization, and weaning [if still intubated]) and at 15 to 30 minutes after discontinuation of VentaProst

[11] For those patients with presence or history of significant restrictive or obstructive lung disease

[12] Vital signs and weight only

Table 2 – Schedule of Assessments and Procedures – Part II

Study Procedures	Screening	Intra-Operative	VentaProst Treatment Period (OR/ICU)	End of Study
Written Informed Consent	X			
Demographics	X			
Assign Patient ID	X			
Medical History	X			
Medication History	X			
Physical Examination	X			X
Vital Signs/Weight/Height	X			X[9]
12-Lead ECG	X			X
Spirometry	X[8]			
Clinical Laboratory Sampling	X			X
Serum Pregnancy Test	X			X
Inclusion/Exclusion Criteria	X	X		
Cardiac Surgery with CPB		X		
Administer VentaProst			X[6]	
Hemodynamic Parameters[1]		X[5]	X[7]	
Oxygenation Measurements[2]			X[7]	
Ventilator Parameters[3]			X[7]	
AE Monitoring[4]		X		X
Concomitant Medications	X	X		X

[1] Hemodynamic parameters include, but not limited to, Cardiac Index (CI), Cardiac Output (CO), Central Venous Pressure (CVP), Diastolic Pulmonary Arterial Pressure (dPAP), Diastolic Systemic Arterial Pressure (dSAP), Heart Rate (HR), Mean Pulmonary Arterial Pressure (mPAP), Mean Systemic Arterial Pressure(mSAP), Pulmonary Capillary Wedge Pressure (PCWP), Pulmonary Vascular Resistance (PVR), Rhythm, Systolic Pulmonary Arterial Pressure (sPAP), and Systolic Systemic Arterial Pressure (sSAP)

[2] Oxygenation measurements include SaO_2 or SpO_2 and PaO_2

[3] Ventilator parameters include Ventilator Type, Ventilator Mode, FiO_2, Inspiratory Time, Mean Airway Pressure, Peak Inspiratory Pressure, Positive End Expiratory Pressure, and Respiratory Rate

[4] To include unanticipated medical events in the judgment of the investigator

[5] Measure hemodynamic parameters prior cardiac surgery with CPB. Prior to dosing with VentaProst, measure hemodynamic, oxygenation, and ventilator parameters

[6] Initiate VentaProst at a starting dose of 3.4 ng/kg/min of VentaProst and titrate VentaProst dose up in 3.4 ng/kg/min increments as clinically indicated (refer to VentaProst Pharmacy Manual); stabilize the patient on final dose of VentaProst

[7] Measure hemodynamic, oxygenation, and ventilator parameters before and after each VentaProstdose change (during dosing, stabilization, and weaning [if still intubated) and at 15 to 30 minutes after discontinuation of VentaProst

[8] For those patients with presence or history significant restrictive or obstructive lung disease

[9] Vital signs and weight only

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LIST OF ACRONYMS, ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
AE	Adverse |Event
ALT (SGPT)	Alanine Aminotransferase (serum glutamic pyruvic transaminase)
AP	Alkaline Phosphatase
AST (SGOT)	Aspartate Aminotransferase (serum glutamic oxaloacetic transaminase)
bpm	Beats Per Minute
BUN	Blood Urea Nitrogen
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
CSR	Clinical Study Report
CVP	Central Venous Pressure (mm Hg)
dPAP	Diastolic Pulmonary Arterial Pressure (mm Hg)
dSAP	Diastolic Systemic Arterial Pressure (mm Hg)
ECG	Electrocardiogram
ETT	Endotracheal Tube
FDA	Food and Drug Administration
FiO_2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
HFNC	High Flow Nasal Cannula
HME	Heat-Moisture Exchanger
HPLC-MS/MS	High-Pressure Liquid Chromatography Coupled to Mass Spectrometry
HR	Heart Rate (bpm)
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute
mPAP	Mean Pulmonary Arterial Pressure (mm Hg)

Abbreviation	Term
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
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
SpO_2	Oxygen Saturation by Pulse Oximetry
SVR	Systemic Vascular Resistance
TEAE	Treatment-Emergent Adverse Event
TEE	Transesophageal Echocardiogram
TPG	Transpulmonary Gradient
ULN	Upper Limit of Normal
WBC	White Blood Cell (count)
WHO	World Health Organization

2. BACKGROUND AND RATIONALE

2.1 Introduction

Aerogen Pharma is developing VentaProst, an inhaled epoprostenol, as an integrated medication/device combination product consisting of a FDA-approved and commercially available epoprostenol sodium intravenous (IV) solution (Flolan®) administered by a precision single-patient use custom nebulizer compatible with ventilator support equipment used in operating rooms (ORs) and intensive care units (ICUs). VentaProst is being investigated as a perioperative pulmonary vasodilator for patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). VentaProst therapy will be transferable from anesthesia ventilator to patient transport to ICU ventilator and on to nasal cannula post-extubation, thus maintaining vasodilation and preventing rebound pulmonary hypertension (PH) during patient transition from surgery.

Flolan (epoprostenol sodium), also known as prostacyclin, PGI_2 or PGX, a metabolite of arachidonic acid, is a naturally occurring prostaglandin. Epoprostenol has two major pharmacological actions: (1) direct vasodilation of pulmonary and systemic arterial vascular beds, and (2) inhibition of platelet aggregation. In animals, the vasodilatory effects of epoprostenol reduce right and left ventricular afterload and increase cardiac output (CO) and stroke volume.

Epoprostenol is rapidly hydrolyzed at neutral blood pH and is also subject to enzymatic degradation. No available chemical assay is sufficiently sensitive and specific to assess the *in vivo* human pharmacokinetics (PK) of epoprostenol. Animal studies using tritium-labelled epoprostenol have indicated a high clearance (93 mL/min/kg), small volume of distribution (357 mL/kg), and a short half-life (2.7 minutes). During infusions in animals, steady-state plasma concentrations of tritium-labelled epoprostenol were reached within 15 minutes and were proportional to infusion rates.

Epoprostenol is metabolized to 6-keto-PGF1α (formed by spontaneous degradation) and 6,15-diketo-13,14-dihydro-PGF1α (enzymatically formed), both of which have pharmacological activity at orders of magnitude less than epoprostenol in animal test systems. 6-keto-PGF1α has been used as a surrogate PK metabolite for epoprostenol, but does not accurately represent the local active concentration of epoprostenol in the lungs with an elimination half-life of approximately 20-30 minutes. Additionally, large and rapid fluctuations in endogenous epoprostenol as indicated by 6-keto-PGF1α levels perioperatively in cardiac surgery confound the exogenous epoprostenol contribution for PK determinations (Ylikorkala 1981).

Inhalation delivery of epoprostenol in cardiothoracic surgery patients offers an attractive alternative to IV delivery because it minimizes systemic exposure associated with clinically hazardous effects such as hypotension and exacerbation of pulmonary and cardiac shunts. The rationale for administering epoprostenol continuously as an aerosol through ventilator support equipment stems from its extremely short half-life of approximately three minutes *in vivo*. This enables delivery of high local concentrations of vasodilator into the lung vasculature, reducing PVR (pulmonary vascular resistance)

and RH (right heart) afterload. As a result, the use and effectiveness of inhaled epoprostenol is widely reported [Buckley and Feldman, 2010; De Wet, 2004; Fattouch, 2005; Fattouch, 2006; Hache, 2003; Haraldsson, 2001; Khan, 2009; Ocal, 2005] in a variety of applications including mitral valve surgery. Nonetheless, such practices remain off-label, as inhaled epoprostenol is not FDA-approved for this indication or route of administration.

Clinical centers have independently developed protocols to deliver the IV formulation as aerosol by mechanical ventilation and nasal cannula using commercially available nebulizers. The nominally prescribed dose of 50 ng/kg/min is administered without regard for system efficiencies with these protocols. This results in dose delivery to the lungs that is assumed to be within the flat portion of the hemodynamic dose response curve to inhaled epoprostenol.

A review of published literature demonstrates that the use of inhaled epoprostenol in patients undergoing cardiothoracic surgery is safe and well tolerated. Doses of 10 – 100 ng/kg/min administered through a wide variety of conventional aerosol delivery methods led to improved hemodynamics (such as lowering of pulmonary arterial pressure [PAP] and pulmonary vascular resistance [PVR]), improved cardiac index (CI) and right ventricular ejection fraction (RVEF), easier separation from CPB, reduced intubation times, and shorter stays in the ICU.

The VentaProst nebulizer delivery platform is designed to accurately and precisely administer aerosol to the lungs of critically ill patients requiring support via mechanical ventilation and/or supplemental oxygen by nasal cannula. The intent is to standardize the critical components for consistent and quantifiable aerosolized epoprostenol delivery by mechanical ventilator and nasal cannula systems. Aerogen Pharma has evaluated various delivery systems used for conventional aerosol administration of epoprostenol to the lungs (in accordance with each site's standard of care practice guideline) and has estimated the equivalent dose by VentaProst.

The intent of Part I of the Phase 2a study is to demonstrate that the estimated VentaProst dose has the same hemodynamic effect as aerosolized Veletri at 50 ng/kg/min (in accordance with each site's standard of care guidelines). The assumption is that the hemodynamic response from the aerosolized Veletri dose will not change significantly with minor changes in dose (flat portion of the dose response curve). When patients are converted to VentaProst, a determination is made whether or not the hemodynamic response is similar by being at least as much as the response with the aerosolized epoprostenol dose. If the hemodynamic response with VentaProst is less than that of the aerosolized Veletri dose, the dose will be increased until a similar response is observed. VentaProst dosing will not be titrated downward to match the aerosolized Veletri hemodynamic response because of the possibility that the patients' requirements for pulmonary vasodilation may have improved since the start of aerosolized Veletri.

Part II of the study is intended to start VentaProst dosing at a dose that will show an improved hemodynamic response by increasing the dose (steep portion of the dose response curve). The intent is to demonstrate that simple dose adjustments to the VentaProst delivery device flow of epoprostenol to the nebulizer can rapidly optimize

VentaProst dose administration.

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.

2.2.3 Summary of Pharmacokinetic Results

Refer to the current IB for pharmacokinetic results with inhaled epoprostenol.

2.2.4 Summary of Clinical Results

There have been no clinical trials to date with VentaProst.

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.

2.2.6 Dosing Rationale for VentaProst

Literature on the current use of aerosolized epoprostenol shows a wide range and technically variable dosing for lowering PVR. Most of the experience is with continuous nebulization by commercially available nebulizers in various positions in mechanical ventilator circuits.

Unlike the commercially available nebulizer systems, VentaProst aerosolizes epoprostenol only during the inspiratory cycle of the ventilator, and administers very consistently sized aerosol droplets in close proximity to the endotracheal tube (ETT) of mechanically ventilated patients.

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to identify the relative dose equivalency between effective conventionally administered aerosolized Veletri and VentaProst doses.

3.2 Secondary Objectives

The secondary objectives are:

- To evaluate the safety and tolerability of VentaProst doses in a patient population post cardiac surgery with cardiopulmonary bypass (CPB)
- To demonstrate that VentaProst dose titration to achieve at least a 15% improvement in one or more hemodynamic parameters (as defined by the clinical team) is safe and effective
- To demonstrate the PD equivalence (based on cardiovascular parameters, indices of oxygenation, and ventilator support) of VentaProst doses to aerosolized Veletri doses
- To identify cardiovascular medications administered concomitantly with VentaProst
- To monitor ventilator support needed

4. OVERALL STUDY DESIGN AND PLAN

4.1 Part I

The first part of this study will be conducted in approximately 10 consented post-operative cardiothoracic surgery patients on CPB who are receiving aerosolized Veletri (in accordance with each site's standard of care guidelines) and who demonstrate at least a 15% improvement in one or more hemodynamic parameters (as defined by the clinical team) when treated with aerosolized Veletri. This part of the study is designed to demonstrate the dose equivalence between aerosolized Veletri and VentaProst using a patient's hemodynamic parameters, with the goal to determine the VentaProst dose necessary to achieve a hemodynamic response that is not less than 90% of the effect observed with 50 ng/kg/min aerosolized Veletri. Arterial oxygen saturation (SaO_2) must be maintained at or above the level obtained with aerosolized epoprostenol administration.

Qualifying patients will:

- Receive aerosolized Veletri 50 ng/kg/min in the OR/ICU
- Have hemodynamic parameters measured before and after aerosolized Veletri administration to determine changes

- *IF AT LEAST A 15% IMPROVEMENT IN ONE OR MORE HEMODYNAMIC PARAMETERS (AS DEFINED BY THE CLINICAL TEAM) IS SEEN WITH AEROSOLIZED VELETRIAFTER STABILIZATION IN THE ICU*:
  - Be administered VentaProst as follows: Setup VentaProst inline to the ventilator circuit, start nebulization, then stop conventional Veletri pump flow and nebulizer while still inline. Do not remove Veletri administration system until VentaProst administration is confirmed
- *IF LESS THAN A 15% IMPROVEMENT IN ONE OR MORE HEMODYNAMIC PARAMETERS (AS DEFINED BY THE CLINICAL TEAM) IS SEEN WITH AEROSOLIZED VELETRI AFTER STABLIZATION IN THE ICU*:
  - Not be administered VentaProst

- Receive a calculated equivalent starting dose of 17 ng/kg/min of VentaProst while still on mechanical ventilation
- Receive increases in the VentaProst dose in 20% increments (refer to the VentaProst Pharmacy Manual) every 15 minutes until at least 90% of the hemodynamic effect observed with 50 ng/kg/min aerosolized Veletri is achieved

Once a VentaProst dose equivalence has been achieved, patients will be weaned from VentaProst. VentaProst weaning will occur from mechanical ventilation only. If the patient has been extubated and is on institution's standard of care delivery system for administering aerosolized Veletri, weaning will occur in accordance with each site's standard of care guidelines for weaning of aerosolized Veletri. The table below shows the typical weaning steps for aerosolized Veletri from mechanical ventilation. If weaning from VentaProst occurs while on mechanical ventilation, doses will be decreased in 20% increments of the VentaProst equivalent dose.

Weaning Guideline

Aerosolized Veletri (from Ventilator)	VentaProst (from Ventilator)
50 ng/kg/min	Dose Equivalence to aerosolized Veletri 50 ng/kg/min
40 ng/kg/min	80% of Dose Equivalence
30 ng/kg/min	60% of Dose Equivalence
20 ng/kg/min	40% of Dose Equivalence
10 ng/kg/min	20% of Dose Equivalence

Patients on mechanical ventilation 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 increments of 20% of the VentaProst equivalent dose, with a minimum of 30 minutes between changes, down to 20% of the dose before discontinuation. The VentaProst weaning process should occur in isolation to other

treatment changes (no changes in inotropes, pressors or vasodilators). Patients will be observed closely before, during, and after dosing changes. In the event patients demonstrate signs of hemodynamic instability (changes in combined hemodynamic parameters) or a decrease in oxygenation indicated by either arterial or central blood oxygenation saturation 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. A final PD measurement will be collected 15 to 30 minutes after discontinuation of VentaProst.

Patients will be monitored for safety and PD efficacy throughout the aerosolized Veletri and VentaProst administrations.

4.2 Part II

The second part of the study will be conducted in approximately 10 consented cardiothoracic surgical patients on CPB with perioperative pulmonary hypertension (mPAP > 25 mm Hg). This part of the study is designed to establish a dose response relationship of VentaProst to PD effect by dose escalation in these patients. The goal will be to determine the VentaProst dose necessary to achieve at least a 15% improvement in one or more hemodynamic parameters (as defined by the clinical team).

Hemodynamic measurements will be taken prior cardiac surgery (after induction) with CPB, prior to dosing with VentaProst, and after each dose titration step.

Qualifying patients will:

- Receive a starting dose of 3.4 ng/kg/min of VentaProst
- Have hemodynamic parameters monitored and recorded
- Receive increase in the VentaProst dose in 3.4 ng/kg/min increments (refer to VentaProst Pharmacy Manual)
    - *IF A GREATER THAN A 15% IMPROVEMENT IN ONE OR MORE HEMODYNAMIC PARAMETERS (AS DEFINED BY THE CLINICAL TEAM) IS SEEN WITH THE INITIAL VENTAPROST DOSE*, but *NO* additional clinically meaningful change is seen with this first dose escalation:
        - Have the VentaProst dose reduced to the initial dose level
    - *IF A GREATER THAN A 15% IMPROVEMENT IN ONE OR MORE HEMODYNAMIC PARAMETERS (AS DEFINED BY THE CLINICAL TEAM) IS SEEN WITH THE INITIAL VENTAPROST DOSE*, but *AN* additional clinically meaningful change is seen with the first dose escalation:
        - Continue to receive VentaProst in increasing steps of 3.4 ng/kg/min every 5 to 15 minutes as clinically indicated until no further improvements in one or more hemodynamic parameters are achieved or until dose-limiting pharmacological effects are elicited or a tolerance limit to VentaProst is established.

- *IF A LESS THAN A 15% IMPROVEMENT IN ONE OR MORE HEMODYNAMIC PARAMETERS (AS DEFINED BY THE CLINICAL TEAM) IS SEEN WITH FIRST DOSE INCREASE*:
  - Continue to receive VentaProst in increasing steps of 3.4 ng/kg/min every 5 to 15 minutes as clinically indicaged until no further improvements in one or more hemodynamic parameters are achieved or until dose-limiting pharmacological effects are elicited or a tolerance limit to VentaProst is established.
  - Reduce the VentaProst dose to the previous dose level (after the VentaProst dose has stabilized) at which the one or more hemodynamic parameters showed maximum improvement. The VentaProst dose level will remain at this setting until clinical conditions determine the need for changing the dose.

Arterial and central venous blood oxygenation parameters will also be considered in the titration process.

Hemodynamic, oxygenation, and ventilator parameters will be obtained at the time of each VentaProst dose adjustment in the ICU.

Patients requiring post-operative support with epoprostenol will be allowed to continue on VentaProst treatment in the ICU as long as they are still on mechanical ventilation. For weaning, doses will be decreased in increments of 20% of the VentaProst equivalent dose, with a minimum of 30 minutes between changes, down to 20% of the dose before discontinuation (see Section 4.1, Weaning Guideline in Part I above). If the patient is extubated and placed on institution's standard of care delivery system for administering aerosolized Veletri, weaning from aerosolized Veletri will follow each institution's guideline.

4.3 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.

4.3.1 Part I

Individual patient participation is expected to be approximately 5 weeks including:

- Screening: up to 30 days
- Intra-Operative: 3-8 hours
- Aerosolized Veletri Treatment administered in accordance with each site's standard of care guidelines (OR/ICU): 24+ hours (dependent on multiple factors)
- VentaProst Treatment (ICU): 24+ hours (dependent on multiple factors)
- End of Study: 4+ hours (dependent on multiple factors)

4.3.2 Part II

Individual patient participation is expected to be approximately 5 weeks including:

- Screening: up to 30 days
- Intra-Operative: 3-8 hours
- VentaProst Treatment (OR/ICU): 24+ hours (dependent on multiple factors)
- End of Study: 4+ hours (dependent on multiple factors)

4.4 Screening

The purpose of Screening is to ensure that each patient meets all the specified inclusion and none of the exclusion criteria.

4.5 Intra-Operative/ICU

In Part I, approximately 10 cardiac surgery patients on CPB who meet entry criteria will be entered into the study and will receive conventionally-administered aerosolized Veletri (in accordance with each site's standard of care guidelines) in the OR or ICU. Once clinically defined hemodynamic effects are achieved in the ICU, the aerosolized epoprostenol will be stopped and patients will be crossed-over to a calculated VentaProst equivalent dose of 17 ng/kg/min. The VentaProst dose will then be increased in 20% increments (refer to VentaProst Pharmacy Manual) every 15 minutes to match the PD measures achieved with the aerosolized Veletri dose.

In Part II, approximately 10 cardiac surgery patients on CPB who meet study entry criteria will be entered into the study and will be assigned to receive a starting dose of 3.4 ng/kg/min of VentaProst in the OR or ICU. The VentaProst dose will then be increased in 3.4 ng/kg/min increments (refer to VentaProst Pharmacy Manual) every 5 to 15 minutes as clinically indicated until no further improvements in one or more hemodynamic parameters are achieved.

4.6 End of Treatment

In both Part I and Part II, final PD measurements (based on hemodynamic parameters, indices of oxygenation, and venilator support) will be collected 15 to 30 minutes after discontinuation of VentaProst. End of study physical examination, vital signs/weight, 12-lead ECG, clinical laboratory testing, serum pregnancy testing, hemodynamic parameters, oxygenation measurements, ventilator parameters, adverse events monitoring, and concomitant medications will also be obtained at the end of treatment.

5. SELECTION AND WITHDRAWAL OF PATIENTS

Approximately 10 patients will be enrolled in each part of this study at approximately three clinical sites in the United States. A minimum of three patients at an individual site will be enrolled in Part I of the study before the site can continue to Part II.

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.

5.1 Inclusion Criteria

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

1. Women and Men 18 to 80 years of age
2. Provide written informed consent
3. Willing and able to comply with all aspects of the protocol
4. For patients in Part I:
    a. Undergo cardiac surgery on CPB (including planned cardiac transplantation)
    b. Clinically require treatment with and receive aerosolized Veletri
    c. Demonstrate a clinically meaningful hemodynamic response to aerosolized Veletri (defined as at least a 15% improvement in one or more hemodynamic parameters [as defined by the clinical team])
5. For patients in Part II:
    a. Undergo cardiac surgery with CPB (including planned cardiac transplantation)
    b. Have perioperative pulmonary hypertension (mPAP > 25 mm Hg)
    c. Clinically require treatment with inhaled epoprostenol

5.2 Exclusion Criteria

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

1. Current smoker (i.e., within the last 30 days)
2. Emergency operative status
3. Upper and/or lower respiratory tract infection within four weeks of screening
4. Contraindication to transesophageal echocardiogram (TEE) including esophageal disease or unstable cervical spine
5. Renal (creatinine > 2.0 mg/dL) or severe hepatic impairment
6. Thromboembolic disease treated with anticoagulant therapy
7. Bleeding disorders
8. Presence or history of significant restrictive or obstructive lung disease (FEV_1 and/or FVC < 60% of predicted normal lung function)
9. History of current malignancy or recurrence of malignancy within two years prior to Screening (not including patients with < 3 excised basal or squamous cell carcinomas)
10. History of a diagnosis of drug or alcohol dependency or abuse within one year
11. Recent history of stroke or transient ischemic attack (within six months prior to Screening) not due to trauma, repaired vascular malformation, or aneurysm
12. Signficantly abnormal laboratory tests at Screening, including:
    a. Alkaline phosphatase (AP), alanine aminotransferase (ALT, SGPT), aspartate aminotransferas (AST, SGOT), or total bilirubin > 2.5X of the

upper limit of normal (ULN)

b. Hemoglobin <9 gm/dL, white blood count (WBC) count <2500 mm^3, neutrophil count <1500 mm^3, platelet count <100 x $10^3/mm^3$
c. Evidence of hemoglobinopathy (including but not limited to sickle cell disease, thalassemia (all variants), hemoglobin M and variants with high oxygen affinity)

13. Pregnant or breastfeeding
14. Participation in an investigational drug, biologic, or investigational cardiac implant study within 30 days preceding the first dose of study medication or plans to take part in another investigational study within 30 days of study completion
15. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with trial participation or investigational product administration or may interfere with the interpretation of trial results and, in the judgment of the Investigator or Sponsor, would make the patient inappropriate for entry into this trial
16. Any condition where aerosolized epoprostenol is contraindicated
17. Known allergy or sensitivity to epoprostenol, any of its ingredients, or the diluent (glycine)

5.3 Re-Screening of Patients

Patients may not be enrolled more than once.

5.4 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.

All patients who discontinue from the study are to complete the End of Study procedures (except Screen Failure patients).

The Investigator will promptly explain to the patient involved 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 CRF.

5.4.1 Criteria for Patient Conversion to Conventional Therapy

At any time during VentaProst administration, patients will be crossed-over to standard of care therapy with aerosolized Veletri if they meet one or more of the following pre-defined criteria for a deterioration in their condition:

- Severe postoperative mediastinal bleeding (> 500 mL/hr)

- Hemoptysis
- If a clinically inadequate response to VentaProst is observed, the patient may be converted back to aerosolized Veletri administered in accordance with each site's standard of care guidelines at the investigator's discretion

Additionally, patients will be crossed-over to standard of care therapy with aerosolized Veletri after extubation.

6. STUDY TREATMENTS

6.1 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 clinical label will identify the product by name, lot number, Sponsor, storage conditions, and indicate that it is limited to investigational use only.

6.1.1 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.

6.2 Treatments Administered

6.2.1 Part I

Post-cardiac surgical patients will initially receive treatment with aerosolized Veletri 50 ng/kg/min in either the OR or the ICU in accordance with each site's standard of care guidelines on administration of aerosolized Veletri. In the ICU, patients who demonstrate at least a 15% improvement in one or more hemodynamic parameters with aerosolized Veletri will be crossed over to a calculated VentaProst equivalent dose of 17 ng/kg/min. The VentaProst dose will then be increased in 20% increments (refer to VentaProst Pharmacy Manual) every 15 minutes to match the clinically meaningful PD measures achieved (i.e., not less than 90% of the effect observed) with the aerosolized Veletri dose.

6.2.2 Part II

In the OR or the ICU, post-cardiac surgical patients will receive VentaProst at a starting dose of 3.4 ng/kg/min ofVentaProst, followed by dose titration up in 3.4 ng/kg/minincrements (refer to VentaProst Pharmacy Manual) every 5 to 15 minutes as clinically indicated until clinically meaningful hemodynamic effects are achieved (i.e., at least a 15% improvement in one or more hemodynamic parameters).

6.3 Study Medication Supply, Preparation, and Administration

6.3.1 Study Medication Supply

The medicinal component of VentaProst, Flolan, will be supplied as a lyophilized

formulation of 1.5 mg of epoprostenol sodium in single-use 17 mL glass vials with gray butyl rubber closures, along with the required sterile diluent buffer for reconstitution in glass vials containing 50 mL of 94 mg glycine, 73.3 mg sodium chloride, sodium hydroxide (added to adjust pH), and Water for Injection, USP.

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

6.3.2 Study Medication Preparation

Refer to the VentaProst 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 48 hours.

During use, a single reservoir of reconstituted solution of epoprostenol sodium can be administered at room temperature for a total duration of eight hours and protect the reconstituted product from temperatures greater than 25ºC (77ºF) and less than 0ºC (32ºF) and do not expose to direct sunlight.

6.3.3 Study Medication Administration

6.3.3.1 Part I

Aerosolized Veletri 50 ng/kg/min will be administered to study patients in the OR or the ICU in accordance with each site's standard of care guidelines on administration of aerosolized Veletri. In the ICU, patients who demonstrate a clinically meaningful hemodynamic response (i.e., at least a 15% improvement in one or more hemodynamic parameters) to aerosolized Veletri will be crossed over to a calculated VentaProst equivalent dose of 17 ng/kg/min to be administered through a custom nebulizer delivery system. The VentaProst dose will then be increased in 20% increments (refer to VentaProst Pharmacy Manual) every 15 minutes to match the clinically meaningful PD measures achieved (i.e., not less than 90% of the effect observed) with the aerosolized Veletri dose.

6.3.3.2 Part II

In the OR or ICU, patients will receive a starting dose of 3.4 ng/kg/min of VentaProst. The VentaProst dose will be titrated up or down in 3.4 ng/kg/min increments (refer to VentaProst Pharmacy Manual) every 5 to 15 minutes as clinically indicated until clinically meaningful hemodynamic effects are achieved (i.e., at least a 15% improvement in one or more hemodynamic parameters).

6.3.4 Study Medication Titration

6.3.4.1 Part I

In the ICU, the VentaProst dose will be increased in 20% increments (refer to VentaProst Pharmacy Manual) every 15 minutes to match the clinically meaningful hemodynamic effects achieved with the conventionally administered aerosolized Veletri. Once clinically meaningful hemodynamic effects are achieved (i.e., not less than 90% of the effect observed), the VentaProst dose will be maintained for at least 15 minutes.

6.3.4.2 Part II

In the OR or ICU, the patient will have their VentaProst dose titrated up in 3.4 ng/kg/min increments (refer to VentaProst Pharmacy Manual) every 5 to 15 minutes as clinically indicated until clinically meaningful PD endpoints are achieved (i.e., at least a 15% improvement in one or more hemodynamic parameters) and the dose stabilized. If the patient fails to achieve clinically meaningful PD endpoints, VentaProst dose escalation will continue until dose-limiting pharmacological effects are elicited or a tolerance limit to VentaProst is established.

6.3.5 Study Medication Weaning

After VentaProst dose stabilization, patients will be weaned from VentaProst. VentaProst weaning will occur from mechanical ventilation only. If the patient has been extubated and is on institution's standard of care delivery for administering aerosolized Veletri, weaning will occur in accordance with each site's standard of care guideline for weaning of aerosolized Veletri.

Patients on mechanical ventilation 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 increments of 20% of the VentaProst equivalent dose, with a minimum of 30 minutes between changes, down to 20% of the dose before discontinuation. The VentaProst weaning process should occur in isolation to other treatment changes (no changes in inotropes, vasopressors or vasodilators). Patients will be observed closely before, during, and after dosing changes. In the event patients demonstrate signs of hemodynamic instability (changes in combined hemodynamic parameters) or a decrease in oxygenation indicated by either arterial or central blood oxygenation saturation 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.

6.4 Identity of the Device Component of the Investigational Product

6.4.1 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.

6.4.1.1 Aerosol Delivery to Ventilated Patients

The Phase 2a VentaProst drug delivery system (Figure 1) consists of reusable and single-patient disposable elements:

- 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, a device to continuously operate the disposable Aerogen Solo nebulizer.
    - Aerogen Pharma Controller, which synchronizes aerosol generation with the ventilator breathing pattern.
    - Aerogen Solo Nebulizer Cable
    - Sensirion Flow Sensor Cable
- Single-patient disposable kit:
    - Aerogen Solo Nebulizer - a low mass and low profile vibrating mesh aerosol generator.
    - Aerogen Continuous Nebulization Tube Set (CNTS) and syringe connected to the nebulizer.
    - Sensirion Flow Sensor.

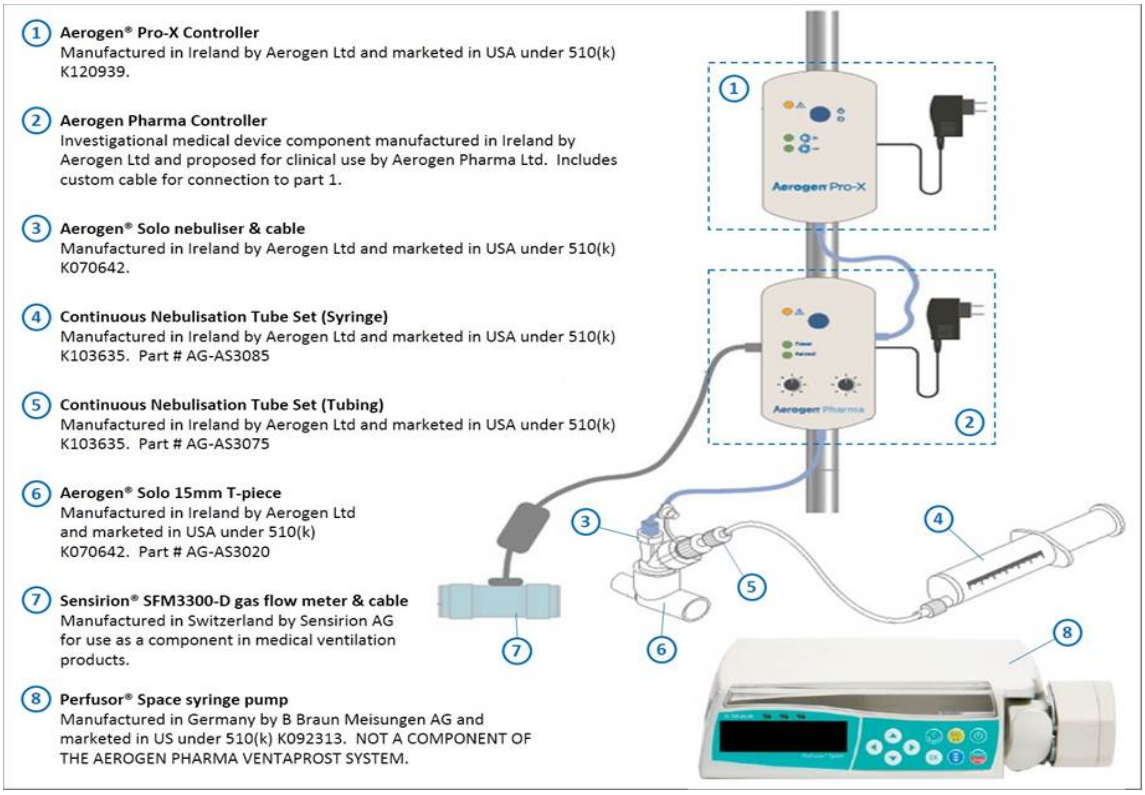

Figure 1 – Drug Delivery System

Prior to VentaProst administration, the study medication will be reconstituted in the recommended diluent buffer and placed into the CNTS syringe. 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 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.

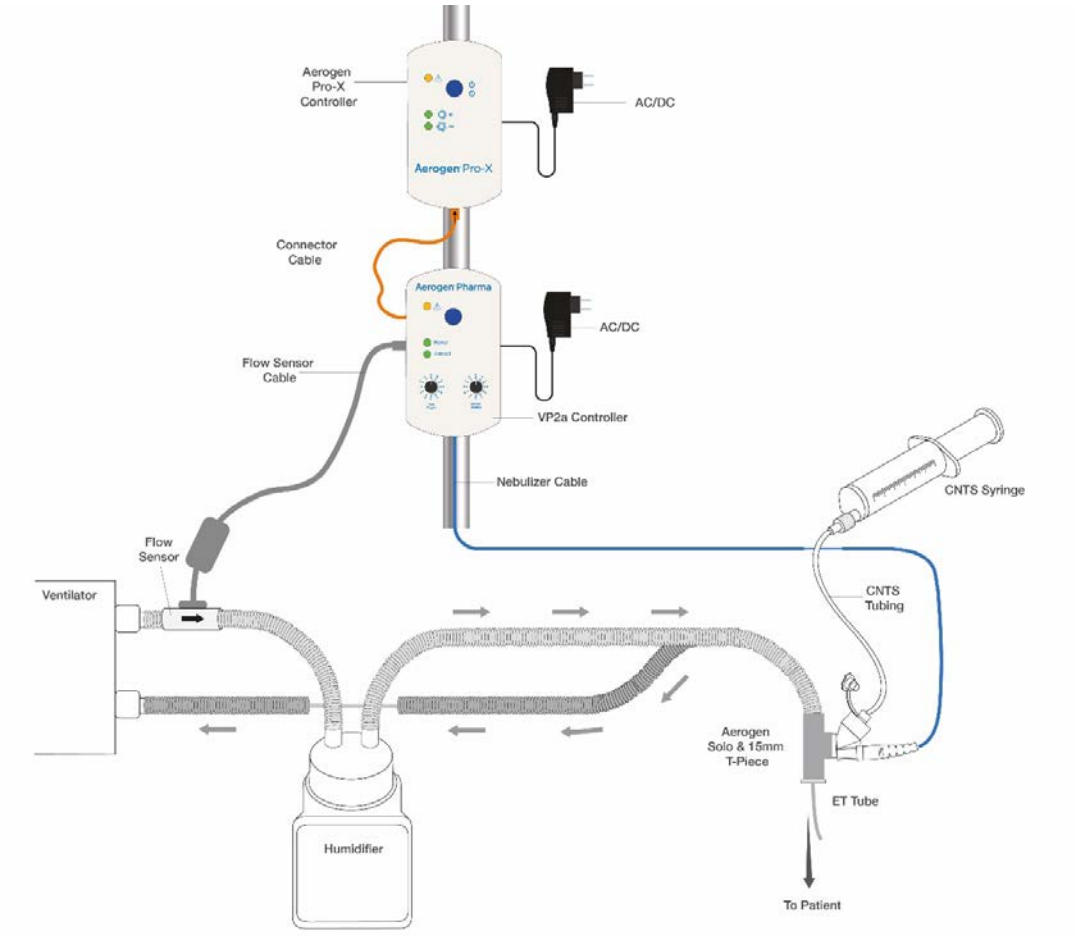

Figure 2 - VentaProst Device Placement in the Gas Pathway

6.4.2 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.

6.4.3 Device Supply

Prior to the first dose of VentaProst for each patient, one delivery device setup will be dispensed. The serial numbers for the controllers, flow sensor, and nebulizer will also be recorded in the dispensing log

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

6.4.4 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 on the appropriate page of the case report form (CRF).
- The investigator suspects the device is not performing optimally for any reason.

6.4.5 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 of more devices need to be replaced, the reason should be documented in the patient's medical record, dispensing log, and eCRF. 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 eCRF.

For device malfunction or complaints, the Sponsor or the Sponsor's designee should be contacted within 48 hours. Failed devices will be inventoried and returned to the Sponsor or the Sponsor's designee.

6.5 Blinding

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

6.6 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 30 days prior) will be recorded on the Prior and Concomitant Therapy eCRF. The Investigator will record any AE on the AE eCRF for which a concomitant medication/therapy was administered.

6.6.1 Prohibited Concomitant Therapy

Not applicable.

6.7 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.

- A signed and dated clinical trial agreement.

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, including empty containers, are to be returned to Aerogen Pharma at the conclusion of the study, unless provision is made by Aerogen Pharma for destruction of supplies and containers at the investigational site. Upon completion of IP accountability and reconciliation procedures by investigational site personnel and documentation procedures by Aerogen Pharma personnel, IP that is to be returned to Aerogen Pharma, if necessary, must be boxed, sealed and shipped back to Aerogen Pharma following all local regulatory requirements.

A Clinical Research Associate (CRA) will review IP accountability during investigational site visits and at the completion of the study.

7. PHARMACODYNAMIC ASSESSMENTS

7.1 Primary Endpoint

Determination of the equivalent dose of VentaProst necessary to achieve a hemodynamic response that is not less than 90% of the effect observed with 50 ng/kg/min aerosolized Veletri.

7.2 Secondary Endpoints

The secondary endpoints that will be assessed include:

- Safety of VentaProst dosing regimen
  - Monitoring of adverse events (AEs), physical examinations, laboratory tests, and electrocardiograms
- Effect of VentaProst dosing regimen on:
  - Cardiovascular Parameters
    - Pulmonary Vascular Resistance (PVR)

    - Pulmonary Arterial Pressure (PAP)
    - Systemic Arterial Pressure
    - Central Venous Pressure (CVP)
    - Pulmonary Capillary Wedge Pressure (PCWP)
    - Cardiac Output (CO)
  - Oxygenation
    - Arterial Oxygen Saturation (SaO_2) or Oxygen Saturation by Pulse Oximetry (SpO_2)
    - Partial Pressure of Oxygen in Arterial Blood (PaO_2)
  - Ventilator Support
    - FiO_2
    - Ventilator pressures
    - Ventilator volumes
    - Duration of intubation
- Number and type of cardiovascular medications required through end of study

7.3 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.

8. SAFETY ASSESSMENTS

Safety will be assessed through monitoring of adverse events (AEs), physical examinations, laboratory tests, and electrocardiograms. Safety assessment frequency is shown in the Schedule of Assessments and Procedures.

8.1 General Safety Procedures

8.1.1 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 as clinically indicated. Weight (kg) will be obtained at the time of Screening and at End of Study. Height will be obtained at the time of Screening.

8.1.2 Physical Examination

Complete physical examination 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. Clinically significant changes from Screening will be recorded as AEs.

8.1.3 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	Hemoglobin, hematocrit, RBC, WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelets
Chemistry	
Electrolytes	Sodium, potassium, chloride, bicarbonate, calcium
Liver function tests	AST, ALT, AP, total bilirubin
Renal function parameters	BUN, creatinine, eGFR calculation
Other	Glucose, albumin, total protein, uric acid, creatine kinase, serum pregnancy test

8.1.4 Electrocardiograms

Twelve-lead electrocardiograms (ECGs) will be obtained at the visits designated on the Schedule of Assessments and Procedures. The Baseline for 12-lead ECGs is Screening.

8.2 Adverse Events

8.2.1 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. Expected medical events are untoward clinical occurrences that are perceived by the investigator to occur with reasonable frequency in the day-to-day care of patients who have undergone cardiac surgery with CPB and who are treated in the ICU with mechanical ventilation. Such events will not be considered adverse events unless the investigator considers the event to be associated with study medication, study device, or to be unexpectedly severe or frequent for a patient.

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 will be recorded and reported as Treatment-Emergent Adverse Events (TEAE). All AEs must be appropriately documented in the patient's medical chart and on the CRFs. 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.

8.2.2 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.

8.2.3 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.

8.2.4 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.

8.2.5 Laboratory Test and other Test Abnormalities as Adverse Events

A laboratory or other test (ECG, 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."

8.2.6 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.

8.2.7 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 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 either telephone the report to the Sponsor's Medical Monitor (contact information found on the Protocol Title Page) or transmit by email a Serious Adverse Event Report (SAER) to the Sponsor's Medical Monitor or the Sponsor's representative. If the initial report is made via telephone, a completed SAER must be emailed within 24 hours of the site's knowledge of the event. Investigational sites will be provided with SAER forms.

The SAE information phoned or 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

The SAER should be emailed within 24 hours with as much of the above information as available at the time. 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.

8.3 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 fax or 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.

9. PHARMACOKINETIC ASSESSMENTS

Not applicable.

10. 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.

10.1 Part I

10.1.1 Screening

Potential study patients will be recruited by the study staff from patients who will undergo cardiac surgery with CPB. Prior to performing any study procedures or assessments, the nature of the study and the potential risks associated with the trial will be explained to the potential study patient and written informed consent obtained. Once informed consent has been obtained, the potential study patient will undergo the following study-related procedures and evaluations:

- Review inclusion and exclusion criteria
- Obtain medical history (including history of any medications within 30 days prior to Screening) and demographics (including date of birth, gender, race, and ethnicity)
- Obtain vital signs (SBP, DBP, HR, respiration rate, and body temperature), height, and weight
- Perform comprehensive physical examination
- Perform 12-lead ECG
- Spirometry – only for those patients with presence or history of significant restrictive or obstructive lung disease
- Collect blood for clinical laboratory tests, including serum pregnancy test for women of childbearing potential.

If the patient satisfies all the eligibility criteria, the patient may be enrolled into the study. If the patient is not eligible for the study, the patient will be considered a screen failure.

Note: Before patients may be switched over to VentaProst, patients must meet Inclusion Criteria 4c, that is, demonstrate a clinically defined response to aerosolized Veletri, defined as at least a 15% improvement in one or more hemodynamic parameters (as defined by the clinical team).

10.1.2 Intra-Operative (OR)

The patient will undergo cardiac surgery with CPB in the OR and the following study-related procedures and evaluations:

- Measure hemodynamic parameters prior to cardiac surgery with CPB. These measurements will represent the baseline for hemodynamic parameters.
- Record all cardiovascular procedures and concomitant medications
- Investigator assessment of any unanticipated medical events

10.1.3 Aerosolized Veletri Treatment (OR/ICU)

If there is a need for administration of aerosolized Veletri, the patient will begin dosing at 50 ng/kg/min (in accordance with each site's standard of care guidelines) and will undergo the following study-related procedures and evaluations:

- Measure hemodynamic, oxygenation, and ventilator parameters before aerosolized Veletri administration and after stabilization of aerosolized Veletri
- If at least a 15% improvement in one or more hemodynamic parameters (as defined by the clinical team) is seen with aerosolized Veletri after stabilization in the ICU, the VentaProst will be set-up inline to the ventilator circuit, VentaProst nebulization will be started, and then the Veletri pump flow will be stopped once VentaProst administration is confirmed. Do not remove Veletri administration system until VentaProst administration is confirmed
- If less than a 15% improvement is seen in one or more hemodynamic parameters (as defined by the clinical team) with aerosolized Veletri after stabilization in the ICU, the patient will not be administered VentaProst
- Record all concomitant medications
- Investigator assessment of any unanticipated medical events

If the patient does not require aerosolized Veletri, or if the patient fails to achieve at least a 15% improvement in one or more hemodynamic parameters with aerosolized Veletri, the patient will be withdrawn from the study as a screen failure.

10.1.4 VentaProst Treatment (ICU)

10.1.4.1 Dosing

Patients who demonstrate at least a 15% improvement in one or more hemodynamic parameters with aerosolized Veletri will be eligible to receive VentaProst. Patients will undergo the following study-related procedures and evaluations:

- Patients will be switched from aerosolized Veletri to receive a calculated equivalent starting dose of 17 ng/kg/min VentaProst while still on mechanical ventilation
- Patients will receive increases in the VentaProst dose in 20% increments (refer to VentaProst Pharmacy Manual) every 15 minutes until at least 90% of the hemodynamic effect observed with 50 ng/kg/min aerosolized Veletri is achieved. Once this has been achieved, the patient will remain on a stable dose of VentaProst for at least15 minutes
- Measure hemodynamic, oxygenation, and ventilator parameters before and after each VentaProst dose
- Record all concomitant medications
- Record AEs

10.1.4.2 Weaning

After the stabilization period, VentaProst weaning procedures will be initiated when the clinical team determines the patient is hemodynamically stable enough to begin the weaning process. VentaProst weaning will occur from mechanical ventilation only. The table below shows the typical weaning steps for aerosolized Veletri from mechanical ventilation. If weaning from VentaProst occurs while on mechanical ventilation, doses will be decreased in 20% increments of the VentaProst equivalent dose. If the patient has been extubated and is on institution' standard of care delivery system for administering aerosolized Veletri, weaning will occur in accordance with each site's standard of care guidelines for weaning of aerosolized Veletri.

Weaning Guideline

Aerosolized Veletri (from Ventilator)	VentaProst (from Ventilator)
50 ng/kg/min	Dose Equivalence to aerosolized Veletri 50 ng/kg/min
40 ng/kg/min	80% of Dose Equivalence
30 ng/kg/min	60% of Dose Equivalence
20 ng/kg/min	40% of Dose Equivalence
10 ng/kg/min	20% of Dose Equivalence

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

VentaProst weaning will be performed as per institutional guidelines for weaning of inhaled Veletri, except that VentaProst doses will be decreased in increments of 20% of the VentaProst equivalent dose, with a minimum of 30 minutes between changes, down to 20% of the dose before discontinuation. The VentaProst weaning process should occur in isolation to other treatment changes (no changes in inotropes, pressors, or vasodilators).

Patients will be observed closely before, during and after dosing changes. In the event the patient demonstrates signs of hemodynamic instability (changes in combined hemodynamic parameters) or a decrease in oxygenation indicated by either arterial or central blood oxygenation saturation during downward titration, the VentaProst dose will be returned to its previous level. Once the patient has been stable for 15 minutes, repeat attempts at dose reduction may be undertaken. The process will continue until the patient is fully weaned from VentaProst. The patient will undergo the following study-related procedures and evaluations during VentaProst weaning:

- Stabilize the patient at each dose adjustment for at least 15 minutes
- Measure hemodynamic, oxygenation, and ventilator parameters before and at 15 to 30 minutes after each VentaProst dose adjustment and at 15 to 30 minutes after discontinuation of VentaProst
- Record all concomitant medications
- Record AEs

10.1.5 End of Study (ICU)

Once VentaProst dosing has been discontinued, the patient will undergo the following study-related procedures and evaluations within 24 hours of VentaProst discontinuation:

- Record all concomitant medications
- Record AEs
- Perform comprehensive physical examination
- Obtain vital signs and weight
- Perform 12-lead ECG
- Collect blood for clinical laboratory tests, including serum pregnancy test for women of childbearing potential

10.2 Part II

10.2.1 Screening

Potential study patients will be recruited by the study staff from patients who will undergo cardiac surgery with CPB. Prior to performing any study procedures or assessments, the nature of the study and the potential risks associated with the trial will be explained to the potential study patient and written informed consent obtained. Once informed consent has been obtained, the potential study patient will undergo the following study-related procedures and evaluations:

- Review inclusion and exclusion criteria

- Obtain medical history (including history of any medications within 30 days prior to Screening) and demographics (including date of birth, gender, race, and ethnicity)
- Obtain vital signs, height, and weight
- Perform comprehensive physical examination
- Spirometry – only for those patients with presence or history of significant restrictive or obstructive lung disease
- Perform 12-lead ECG
- Collect blood for clinical laboratory tests, including serum pregnancy test for women of childbearing potential

If the patient meets all the eligibility criteria, the patient may be enrolled into the study. If the patient is not eligible for the study, the patient will be considered a screen failure.

10.2.2 Intra-Operative (OR)

The patient will undergo cardiac surgery with CPB in the OR and the following study-related procedures and evaluations:

- Measure hemodynamic parameters prior to cardiac surgery (after induction) with CPB. These measurements will represent the baseline for hemodynamic parameters
- Record all cardiovascular procedures and concomitant medications
- Investigator assessment of any unanticipated medical events

10.2.3 VentaProst Treatment (OR/ICU)

10.2.3.1 Dosing

The patient will undergo the following study-related procedures and evaluations:

- Patients will receive a starting dose of 3.4 ng/kg/min of VentaProst
- Patients will receive increases in VentaProst dose by 3.4 ng/kg/min (refer to VentaProst Pharmacy Manual)
    - If greater than a 15% improvement in one or more hemodynamic parameters (as defined by the clinical team) is seen with the initial VentaProst dose, but NO additional clinically meaningful change is seen with the first dose escalation, the VentaProst dose will be reduced to the initial dose level
    - If greater than a 15% improvement in one or more hemodynamic parameters (as defined by the clinical team) is seen with the initial VentaProst dose, but AN additional clinically meaningful change is seen with the first dose escalation, continue to dose with VentaProst in increasing steps of 3.4 ng/kg/min every 5 to 15 minutes as clinically indicated until no further improvements in one or more hemodynamic

parameters are achieved or until dose-limiting pharmacological effects are elicited or a tolerance limit to VentaProst is established

- If less than a 15% improvement in one or more hemodynamic parameters (as defined by the clinical team) is seen with first dose increase, continue to dose with VentaProst in increasing steps of 3.4 ng/kg/min every 5 to 15 minutes as clinically indicated until no further improvements in one or more hemodynamic parameters are achieved or until dose-limiting pharmacological effects are elicited or a tolerance limit to VentaProst is established. After the VentaProst has been stabilized, reduce the VentaProst dose to the previous dose level at which a hemodynamic parameter showed maximum improvement. The VentaProst dose level will remain at this setting until clinical conditions determine the need for changing the dose

- Measure hemodynamic, oxygenation, and ventilator parameters at each dose adjustment
- Record all concomitant medications
- Record AEs

10.2.3.2 Weaning (ICU)

After the stabilization period, VentaProst weaning procedures will be initiated when the clinical team determines the patient is hemodynamically stable enough to begin the weaning process. VentaProst weaning will occur from mechanical ventilation only. The table below shows the typical weaning steps for aerosolized Veletri from mechanical ventilation. If weaning from VentaProst occurs while on mechanical ventilation, doses will be decreased in 20% increments of the VentaProst equivalent dose. If the patient has been extubated and is on institution's standard of care delivery system for administering aerosolized Veletri, weaning will occur in accordance with each site's standard of care practice guidelines for weaning of aerosolized Veletri.

Weaning Guideline

Aerosolized Veletri (from Ventilator)	VentaProst (from Ventilator)
50 ng/kg/min	Dose Equivalence to aerosolized Veletri 50 ng/kg/min
40 ng/kg/min	80% of Dose Equivalence
30 ng/kg/min	60% of Dose Equivalence
20 ng/kg/min	40% of Dose Equivalence
10 ng/kg/min	20% of Dose Equivalence

Patients on mechanical ventilation will be weaned from VentaProst slowly due to concern that VentaProst is providing significant clinical benefit and to avoid a rebound effect. VentaProst weaning will be performed as per institutional guidelines for weaning of

inhaled Veletri, except that VentaProst doses will be decreased in increments of 20% of the VentaProst equivalent dose, with a minimum of 30 minutes between changes, down to 20% of the dose before discontinuation. The VentaProst weaning process should occur in isolation to other treatment changes (no changes in inotropes, pressors, or vasodilators).

Patients will be observed closely before, during and after dosing changes. In the event the patient demonstrates signs of hemodynamic instability (changes in combined hemodynamic parameters) or a decrease in oxygenation indicated by either arterial or central blood oxygenation saturation during downward titration, the VentaProst dose will be returned to its previous level. Once the patient has been stable for 15 minutes, repeat attempts at dose reduction may be undertaken. The process will continue until the patient is fully weaned from VentaProst. The patient will undergo the following study-related procedures and evaluations during VentaProst weaning:

- Stabilize the patient at each dose adjustment for at least 15 minutes
- Measure hemodynamic, oxygenation, and ventilator parameters before and at 15 to 30 minutes after each VentaProst dose adjustment and at 15 to 30 minutes after discontinuation of VentaProst
- Record all concomitant medications
- Record AEs

10.2.4 End of Study (ICU)

Once VentaProst dosing has been discontinued, the patient will undergo the following study-related procedures and evaluations within 24 hours of VentaProst discontinuation:

- Record all concomitant medications
- Record AEs
- Perform comprehensive physical examination
- Obtain vital signs and weight
- Perform 12-lead ECG
- Collect blood for clinical laboratory tests, including serum pregnancy test for women of childbearing potential

11. DATA QUALITY ASSURANCE

11.1 Data Collection

Investigator or designee will enter the information required by the protocol onto the eCRFs in accordance with the eCRF Completion Guidelines that are provided with the eCRFs. CRAs will visit each investigational site as frequently as documented in the monitoring plan to review the eCRFs for completeness and accuracy against the source documents. CRAs will highlight any discrepancies found in the documentation of study conduct and ensure that appropriate site personnel address the discrepancies.

11.2 Clinical Data Management

Data from eCRFs will be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

11.3 Database Quality Assurance

All databases will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be documented and returned to the investigational site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail.

12. STATISTICAL CONSIDERATIONS

12.1 Statistical Methods

A Statistical Analysis Plan will be developed that describes in detail the statistical methods to be used for analysis of this study and will be finalized prior to database lock.

12.2 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 exposure to this investigational product.

12.3 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. Individual patient listings of data will also be provided to allow for review of all pharmacodynamic, safety, and tolerability parameters.

12.4 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. Baseline hemodynamic parameters will be obtained prior to cardiac surgery with CPB.

12.5 Pharmacodynamic Analyses

12.5.1 Primary Endpoint

The primary efficacy endpoint of this study is to determine the equivalent dose of VentaProst necessary to achieve a hemodynamic parameter measurement that is not less than 90% of the effect observed with 50 ng/kg/min aerosolized Veletri.

Further details will be included in the Statistical Analysis Plan.

12.5.2 Secondary Endpoints

Key secondary endpoints include:

- Safety of VentaProst dosing regimen
  - Monitoring of AEs, physical examinations, laboratory tests, and electrocardiograms
- Effect of VentaProst dosing regimen on:
  - Cardiovascular Parameters
    - Pulmonary Vascular Resistance (PVR)
    - Pulmonary Arterial Pressure (PAP)
    - Systemic Arterial Pressure
    - Central Venous Pressure (CVP)
    - Pulmonary Capillary Wedge Pressure (PCWP)
    - Cardiac Output (CO)
  - Oxygenation
    - Arterial Oxygen Saturation (SaO_2) or Oxygen Saturation by Pulse Oximetry (SpO_2)
    - Partial Pressure of Oxygen in Arterial Blood (PaO_2)
  - Ventilator Support
    - FiO_2
    - Ventilator pressures
    - Ventilator volumes
    - Duration of intubation
  - Number and type of cardiovascular medications required through end of study

Similar analyses for the primary endpoint will be applied to the key secondary efficacy endpoints.

12.6 Extent of Exposure

Exposure data will be summarized by treatment group using frequencies and percentages.

12.7 Safety Analyses

Safety measurements include AEs, physical examination, vital signs, laboratory tests, and electrocardiograms. Safety data will be summarized by treatment group using frequencies and incidence rates.

12.7.1 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 CSR.

AEs will be summarized by presenting, for each treatment group, 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.

12.7.2 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.

12.7.3 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 by treatment group.

12.8 The Procedure for Revising the Statistical Analysis Plan

Any changes to the statistical analysis plan will be formalized and dated in an amendment and documented in the CSR.

13. ADMINISTRATIVE PROCEDURES AND INSTRUCTIONS

13.1 Ethics

13.1.1 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 study medication 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.

13.1.2 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).

13.1.3 Patient Information and Informed Consent

As part of administering the informed consent document, the Investigator must explain to each patient 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 should understand the statement before signing and dating it and will be given a copy of the signed document. The patient 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.

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 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.

13.2 Administrative Procedures

13.2.1 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 Sponsor's 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.

13.2.2 Adherence to the Protocol

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

13.2.3 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 assigned CRA. The Investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCPs and local regulatory requirements. The CRFs and patient's corresponding original medical records (source documents) are to be fully available for review by the Sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with federal regulations and

local regulations. All records at the investigational site are subject to inspection by the FDA.

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, polysomnographs, 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.

13.2.4 Recording of Data

In order to provide the Sponsor with accurate, complete, and legible case reports, the following criteria are to be maintained. The Investigator will enter the information required by the protocol onto the eCRFs in accordance with the eCRF Completion Guidelines provided by the Sponsor.

13.2.5 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 eCRFs, Investigator's Brochure, regulatory agency registration documents, e.g., FDA 1572 form, ICFs, and IRB/IEC correspondence. In addition, the Sponsor will send a list of treatment codes by study patient to the Investigator after the clinical database for this study has been secured.

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.

13.2.6 Auditing Procedures and Inspection

In addition to the routine monitoring procedures, the Sponsor's Quality Assurance department or representative conducts audits of clinical research activities in accordance with the Sponsor's or representative's SOPs to evaluate compliance with the principles of ICH GCPs and all applicable local regulations. A government regulatory authority may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator must inform the Sponsor immediately that this request has been made.

13.2.7 Handling of Investigational Product

All IP will be supplied to the Principal Investigator (or designated pharmacist) by the Sponsor or Sponsor representative. 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 CRA 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.

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 product and provide a copy of the completed IP accountability logs to the Sponsor or Sponsor's Designee.

13.2.8 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.

13.2.9 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).

13.2.10 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a trial is prematurely terminated or suspended, the Sponsor should promptly inform the Investigator/Institution and the regulatory authority(ies) of the termination or suspension, and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided the reason(s) for the termination or suspension by the Sponsor or by the Investigator/Institution, as specified by the applicable regulatory requirement(s).

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.

13.2.11 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.

14. REFERENCES

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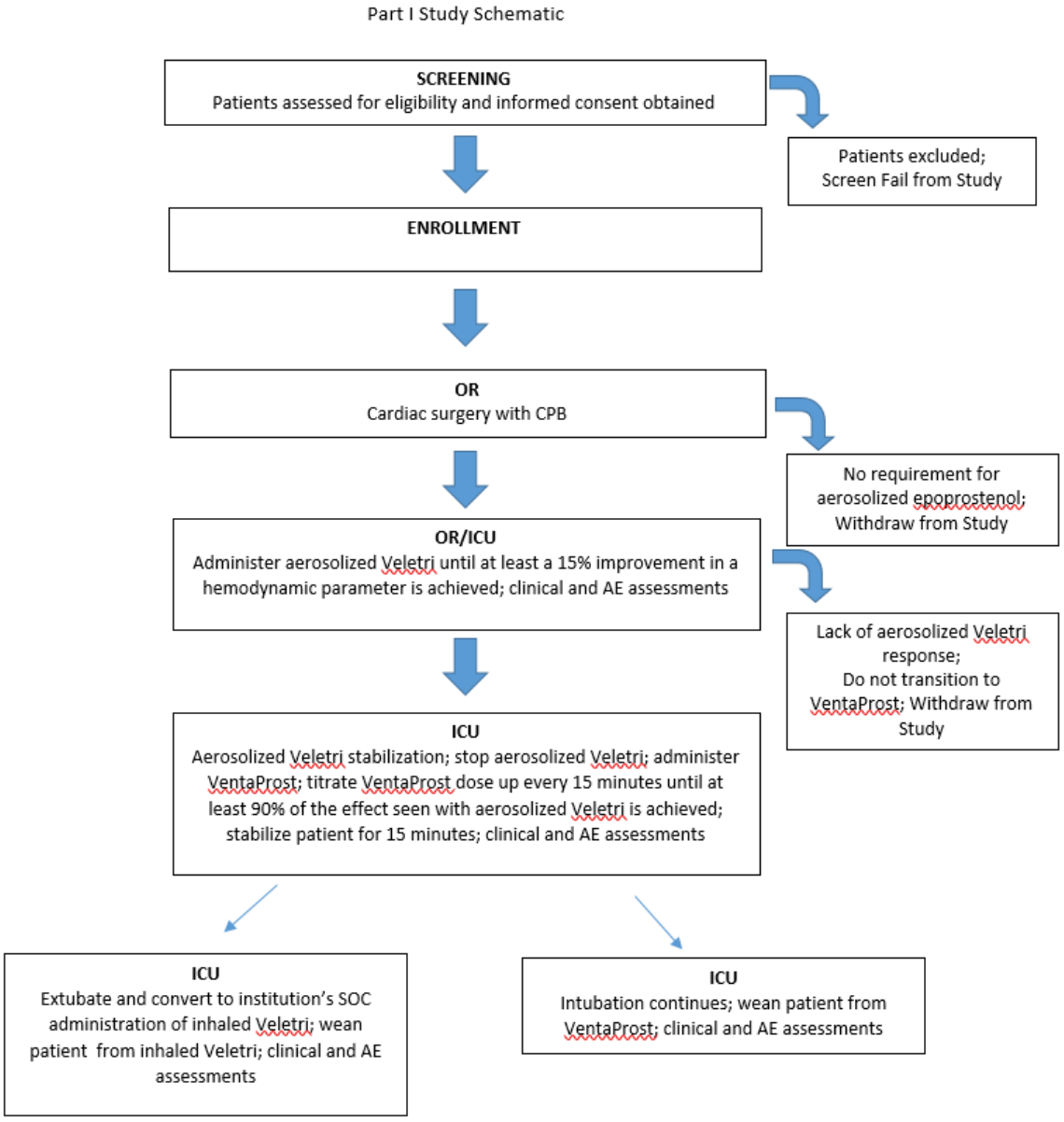
15. APPENDICES

Appendix 1 Part I Study Design Schematic



Appendix 2 Part II Study Design Schematic