PROTOCOL: TNX-LVO-04

TITLE:	**A Double-Blind, Randomized, Placebo-Controlled Study of Levosimendan in Pulmonary Hypertension Patients with Heart Failure and Preserved Left Ventricular Ejection Fraction (PH-HFpEF)**
DRUG:	Levosimendan (Simdax) Injection
IND NUMBER:	IND 47,025
NCT NUMBER:	NCT03541603
SPONSOR*:	Tenax Therapeutics, Inc. One Copley Parkway Morrisville, NC 27560 info@tenaxthera.com
PRINCIPAL/ COORDINATING INVESTIGATOR:	Stuart Rich, MD Professor of Medicine, Northwestern U. Feinberg School of Medicine; Director, Pulmonary Vascular Disease Program
PROTOCOL VERSION AND DATE:	Version 4.0, 15 May 2019

*Tenax Therapeutics, Inc. (Tenax): The term "Sponsor" is used throughout the protocol to represent this legal entity.

This study will be conducted under Food & Drug Administration IND regulations (21 CFR Part 312).

PROTOCOL SIGNATURE PAGE

Sponsor's Approval

Signature: 	**Date:** May 15, 2019
Kevin Crawford, MS Associate Director, Clinical Operations Tenax Therapeutics, Inc	
Signature: 	**Date:** May 15, 2019
Douglas Hay. PhD EVP, Regulatory Affairs Tenax Therapeutics, Inc	

Principal Investigator's Approval

Signature: 	**Date:** May 15, 2019
Stuart Rich, MD Professor of Medicine, Northwestern U. Feinberg School of Medicine; Director, Pulmonary Vascular Disease Program	

Investigator's Acknowledgement

I have read this protocol no. TNX-LVO-04

Title: A Double-Blind, Randomized, Placebo-Controlled Study of Levosimendan in Pulmonary Hypertension Patients with Heart Failure and Preserved Left Ventricular Ejection Fraction (PH-HFpEF)

I have fully discussed the objective(s) of this study and the contents of this protocol with the Sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonization guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to my participation as an Investigator for this study to be terminated.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from the study I will communicate my intention immediately in writing to the Sponsor.

Name of Principal Investigator	Signature of Principal Investigator

Date

LIST OF STUDY CONTACTS

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TABLE OF CONTENTS

ABBREVIATIONS

6MWT	6-minute walk test	ICH	International Conference on Harmonization
AE	adverse event		
ANCOVA	analysis of covariance	IND	Investigational New Drug
BMI	body mass index	IRB	Institutional Review Board
BUN	blood urea nitrogen	ITT	intention-to-treat
CABG	coronary artery bypass graft	IWRS	Interactive Web Response System
CADD	Continuous ambulatory delivery device	IV	intravenous
CDER	Center for Drug Evaluation and Research	MedDRA	Medical Dictionary for Regulatory Activities
CFR	Code of Federal Regulations	PCI	Percutaneous coronary intervention
CK	Creatine kinase	NDA	New Drug Application
C_{max}	maximum plasma concentration	PD	Pharmacodynamic
C_{min}	minimum plasma concentration	PH	Pulmonary hypertension
CRA	Clinical Research Associate	PK	pharmacokinetic
eCRF	electronic Case Report Form	PP	per-protocol
CRO	Contract Research Organization	QoL	quality of life
ECG	electrocardiogram	RBC	red blood cell
EMA	European Medicines Agency	SAE	serious adverse event
FDA	Food and Drug Administration	SAP	Statistical Analysis Plan
eGFR	estimated glomerular filtration rate	SBP	systolic blood pressure
GCP	Good Clinical Practice	SmPC	Summary of Product Characteristics
HCG	human chorionic gonadotropin	TAPSE	Tricuspid annular plane systolic excursion
HFpEF	heart failure with preserved ejection fraction	t_{max}	time to maximum plasma concentration
HIPAA	Health Insurance Portability and Accountability Act	TMF	Trial Master File
IB	Investigator's Brochure	WBC	white blood cell

STUDY SYNOPSIS

Sponsor/Company Tenax Therapeutics, Inc.		
Finished product: Simdax (levosimendan) injection		
Active ingredient: (-)-(R)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono] propanedinitrile		
Study code: TNX-LVO-04	**Date: 15 May 2019; Version 4.0**	
Study title: A Double-Blind, Randomized, Placebo-Controlled Study of Levosimendan in Patients with Pulmonary Hypertension with Heart Failure and Preserved Ejection Fraction (PH-HFpEF)		
Investigators and study centers: Multicenter study (target 20-25 sites in the United States)		
Development phase: 2		
Objectives: To evaluate the efficacy and safety of intermittent levosimendan compared with placebo in hemodynamic improvement with exercise in PH-HFpEF subjects.		
Methodology: Enrolled PH-HFpEF subjects will receive a lead-in 24-hour levosimendan infusion to determine their hemodynamic response and eligibility for the double-blind phase of the study. A total of 36 "responders" will be randomized in the double-blind, placebo-controlled phase. "Responders" will be identified as those subjects with a ≥4mmHg reduction in PCWP during bicycle exercise (25 watts) and no more than a 10% decrease in cardiac index between the baseline measurements and repeated measurements following the initial infusion. Study drug will be administered via i.v. infusion over 24 hours weekly through Week 5 via a PICC line. Infusions (Week 2-5) will be done in the subject's home by a study nurse. Patients will return to the study site for a visit between the Week 3 Week 4 infusions for assessment of subject safety/response and need for dose adjustment. Each subject will return on Week 6 for assessment of efficacy and safety on study drug. A right heart catheter will be inserted to obtain hemodynamic measurements at rest and exercise at baseline, the following day after the lead-in 24-hour infusion, and during Week 6. All subjects randomized will have the opportunity to participate in an Open-label protocol extension.		
Sample size: During the Lead-in phase of the study, a sufficient number of subjects will be enrolled and receive levosimendan to identify a total of 36 'responders'. The levosimendan 'responders' will be randomized 1:1, levosimendan or placebo, for the double-blind phase of the study.		

Diagnosis and main criteria for inclusion and exclusion:

Patients must meet the following criteria to be enrolled in the study:

Inclusion Criteria:

Enrollment Criteria:

1. Men or women, ≥18 years of age
2. Confirmed diagnosis of WHO Group 2 Pulmonary Hypertension (PH) with heart failure and preserved ejection fraction (HFpEF).
3. WHO Group 2 Pulmonary Hypertension subjects with heart failure and preserved ejection fraction as defined by:
    a. Mean pulmonary arterial pressure (mPAP) ≥35 mmHg at rest or with legs up (at baseline right heart catheter/Lead-In)
    b. Pulmonary capillary wedge pressure (PCWP) ≥20 mmHg at rest or with legs up (at baseline right heart catheter/Lead-In)
    c. NYHA Class II or III
    d. LVEF ≥40% by echocardiogram within three months of enrollment with no change in clinical status suggesting the potential for deterioration in systolic function
4. Signed (by the subjects or their legally acceptable representatives) informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.
5. Ability to walk at least 50 meters, but not more than 550 meters in a six-minute walk test.
6. Long term oxygen treatment (if applicable) must be stable for 30 days prior to enrollment.
7. Subjects on a chronic medication or therapy for any underlying cardiac condition must be on a stable dose for ≥30 days prior to randomization, with the exception of diuretics and antihypertensive medication for blood pressure control which may be discontinued if deemed appropriate.
8. Subjects on chronic medications for any underlying respiratory condition must be on a stable dose for ≥30 days prior to randomization

Note: With regard to Inclusion Criteria 6-8, “stable” refers to changes in oxygenation therapy or medications no greater than a 100% increase or a 50% decrease, as needed to optimize the patient.

Randomization Criterion:

9. Response to Lead-in Levosimendan: Patients who demonstrate a ≥4mmHg reduction in PCWP from baseline measured during bicycle exercise (25 watts) with no more than a 10% decrease from baseline in cardiac index following the 24-hr infusion of levosimendan.

Exclusion Criteria:

1. Previous PCI or cardiac surgery (CABG) unless documented to have a negative stress test within the last 12 months.
2. Clinically symptomatic mitral or aortic valvular heart disease.
3. Cardiac index greater than 4.0 L/min/m^2
4. In the opinion of the Principal Investigator, the subject has a primary diagnosis of PH other than WHO Group 2 PH-HFpEF
5. Congenital heart disease other than surgically corrected pre and post tricuspid shunts for at least 5 years
6. Symptomatic coronary artery disease based on a positive stress test.
7. Patients planning lung or heart transplant; or cardiac surgery in the next 4 months
8. Patients diagnosed with pulmonary hypertension associated with clinically significant lung disease at the time of initial diagnosis, or patients with a congenital defect of the lung.
    a. Clinically significant obstructive lung disease is defined as FEV1/FVC <60% of predicted, unless a high resolution chest CT scan shows no more than mild areas of emphysematous changes.
    b. Clinically significant restrictive lung disease is defined as a FVC of <60% of predicted, unless a high resolution chest CT scan shows no more than mild areas of interstitial lung disease or pulmonary fibrosis.
9. Dialysis at randomization (either hemodialysis, peritoneal dialysis, continuous venovenous hemofiltration, or ultrafiltration)
10. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2
11. Liver dysfunction with Child Pugh Class B or C (see Attachment 3)
12. Evidence of systemic bacterial, systemic fungal, or viral infection in last 2 weeks
13. Weight >150 kg
14. Symptomatic low systolic blood pressure (SBP) that cannot be managed to ensure SBP ≥ 100 mmHg at initiation of study drug

15. Heart rate ≥ 100 bpm with study drug, symptomatic and persistent for at least 10 minutes at Lead-in.
16. Hemoglobin < 80 g/L
17. Serum potassium < 3.0 mmol/L or > 5.5 mmol/L at baseline
18. Pregnant, suspected to be pregnant, or breast-feeding
19. Known allergic reaction or sensitivity to levosimendan or excipients.
20. A history of Torsades de Pointes
21. Received levosimendan within 30 days before the planned start of study drug
22. Received an experimental drug or used an experimental medical device within 30 days before the planned start of study drug
23. Concomitant administration of pulmonary vasodilator therapy, or taken within 14 days of randomization
24. Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator
25. Inability to comply with planned study procedures

Investigational product, dose and mode of administration:

Lead-in Phase

Levosimendan, supplied as a concentrated solution (2.5 mg/mL), will be mixed with diluent and administered intravenously at 0.10 µg/kg/min for 24 hours ±30 min.

Double-blind Phase

Study drug concentrated solution (2.5 mg/mL), levosimendan or placebo, will be mixed with diluent and administered via a PICC line as weekly infusions at 0.075 µg/kg/min for 24 hrs. Patients will have a dose escalation between Weeks 4 and 5 (0.10 µg/kg/min for 24 hrs) unless there has been a meaningful change in blood pressure or heart rate (Attachment 5). Infusion rates may be reduced to 0.05 µg/kg/min if the higher dose is not well-tolerated at any time during the initial 5 weeks.

Concomitant Therapy: All subjects must be optimally managed on diuretics and oxygen therapy as indicated by standard of care. Concomitant administration of pulmonary vasodilators is NOT permitted. Patients must not have taken any pulmonary vasodilators within 30 days of enrolment.

Duration of treatment: The first 36 subjects responding to the open-label lead-in 24-hour 0.10 µg/kg/min levosimendan infusion, in the absence of significant hypotension or tachycardia, will be randomized to levosimendan or placebo (1:1). A PICC line will be placed prior to randomization. Randomized subjects will receive weekly home infusions of study drug on Week 2 and 3 at 0.075 µg/kg/min for 24 hours. Patients will have a dose escalation between Weeks 4 and 5 (0.10 µg/kg/min for 24 hrs) unless there has been a meaningful change in blood pressure or heart rate.

Reference product, dose and mode of administration: Matching placebo.

Criteria for Evaluation:

Primary Endpoint:

- Change from baseline PCWP during bicycle exercise (25 watts) at Week 6

Secondary Endpoints:

- Change in Cardiac Index at rest and with exercise at Week 6
- Change in PVR effect at rest and with exercise at Week 6
- Change in PCWP when supine and legs elevated at Week 6
- Patient global assessment (based on a six-point Likert scale) at Week 6
- Exercise duration 6-min walk test at Week 6
- Physician's Assessment of Functional Class
- Clinical Events: Death and hospitalizations

Exploratory Endpoint:

- Change in echo measurements of RV size and TAPSE

Evaluation and statistical methods:

A total of 36 randomized subjects (at 1:1 levosimendan vs. placebo) will provide ≥80% power to detect the difference at two-sided 0.05 level, assuming a SD=5mmHg in PCWP and a treatment difference of ≥4.81 mmHg.

The primary analysis will be on the Full Analysis Set, defined as those subjects that received study drug and completed their Week 6 office visit. Hemodynamic responses during the initial lead-in infusion will be summarized using descriptive statistics for all subjects receiving levosimendan and in PH-HFpEF subgroups.

The hemodynamic variables will be analyzed using ANCOVA with effects for treatment and investigative site. A sensitivity analysis will include an adjustment for baseline. An additional analysis will be performed on the per protocol set that completed the study without major protocol deviations.

All secondary analyses will be performed in the Full Analysis Set and PP Analysis Set. Exercise tolerance differences will be tested using an ANOVA with effects for treatment and investigative site. Treatment differences in the Patients response identified by Likert Scale will be analyzed by a Mann–Whitney–Wilcoxon test.

TIME AND EVENTS SCHEDULE

Study Phase/ Event	**Screening**	**Lead-In Infusion**	**Weeks 2-5 (± 48 hrs.)**	**Interim Office Visit**	**Week 6 (3-6 days following completion of the Week 5 infusion.)**
	≤ 28 Days Prior to Day 0	**Day 0 (Visit 1)[15]**	**Weekly Infusion (Visit 2, 3, 4, 5)[11, 15]**	**Between Week 3 and Week 4[12]**	**Office Visit (Visit 6)[11]**
Informed Consent	X				
Inclusion / Exclusion	X				
History of Qualifying Hemodynamics	X				
Medical History	X				
Physical Examination	X				
Body Weight	X	X		X	
Urine Pregnancy Test[1]	X				
Serum Chemistry & Hematology – Local Lab	X				X
Child Pugh Class	X				X
Vital Signs	X	X	X	X	X
Electrocardiogram (EKG)	X				X
Echocardiography[2]	X				X
Lead-in Dose[3]		X			
Randomization		X			
Study Drug Administration[4]			X		
Right Heart Cath and Hemodynamics[5]		X			X
PICC line insertion[6]		X			
Dose Escalation			X[13]		
Quality of Life (Likert)[7]				X	X
NYHA Functional Class	X			X	X
6 - Minute Walk Test[8]	X			X	X
Adverse Events/SAEs	X	X	X	X	X
Concomitant Procedures		X	X	X	X
Concomitant Medications		X	X	X	X
PK Sample[9]		X			X
Genotyping Sample[10]		X			
Arrhythmia Monitoring	X[14]		X[14]		

Footnotes for Time and Events Schedule

1. Pregnancy tests for women of childbearing potential only. Additional serum or urine pregnancy testing may be performed as required by local regulations (if performed, pregnancy tests must be negative for subjects to continue in the study). Pregnancy test results must be available before study drug administration.
2. Echocardiography or measurement of ventricles.
3. Lead-in dose may be performed on same day as Screening Visit procedures.
4. Week 2, 3, 4, and 5. Confirm that the subject's diuretic dose has remained consistent in the last week.
5. Invasive hemodynamics will be assessed via a right heart catheter. A Swan-Ganz catheter will be inserted via the internal jugular (right or left) or subclavian vein (right or left). Hemodynamic measurements and determinations include: cardiac index (CI), cardiac output (CO), mean pulmonary artery pressure (mPAP), and pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP, pulmonary vascular resistance (PVR), stroke volume index (SVI), stroke volume (SV). Measurements will be taken initially when the subject is supine, legs elevated and at supine bicycle exercise (25 watts). A levosimendan-treated subject will be identified as a responder if there is a 4mmHg reduction in PCWP (with the cardiac index the same or increased) at the end of the 24-hr acute infusion. (see Attachment 6)
6. PICC line insertion will occur only for those patients randomized to the double-blind portion of the study
7. Likert Scale should be completed at Interim Office Visit and at Week 6
8. 6-min walk test will be conducted according to ATS Statement: Guidelines for the Six-Minute Walk Test
9. Blood samples will be taken at the end of study drug infusion (24 ± 2 hours). An additional sample for pharmacokinetic analysis will be collected at Week 6 or upon termination from the study, whichever comes first. PK samples will be sent to a central laboratory. A separate blood sample will be collected for acetylation status genotyping at the end of study drug infusion.
10. Blood sample will be collected for analysis of acetylation status. No further testing on these samples will be conducted
11. Visits at Weeks 2, 3, 4, 5, and 6 should occur within ±48 hours of the scheduled visit (section 8.4).
12. This office should occur within 48 hours prior to the Week 4 infusion for assessment of performance and safety (see section 8.5).
13. Subjects will have a dose escalation between Weeks 4 and 5 (0.10 µg/kg/min for 24 hrs.) unless there has been a meaningful change in blood pressure or heart rate (Attachment 5). The home health care nurse will be notified by the site to confirm up-titration or any dose adjustments.
14. Arrhythmia monitoring will be performed at Screening and Week 5. An electronic monitoring device will be applied for approximately 72 hours prior to the Lead-In dose. At Week 5, the device is to be applied prior to (< 1 hour) the 24-hour infusion and will collect data over the following 72 hours (approximately).
15. Subjects who receive levosimendan during the Lead-In dose but are not randomized into the trial, will be followed for safety for 2 weeks post end of 24-hour infusion. A phone contact will be made to the subject at 24 hours, 7 days, and 14 days post infusion by investigational site personnel to assess adverse events. Please see section 8.7 for further details regarding subjects who terminate the study early.

1. BACKGROUND INFORMATION

1.1 Condition Background and Current Treatment

Heart failure with preserved ejection fraction (HFpEF) is the most common form of heart failure, representing about 50% of all heart failure cases and increasing out of proportion to the incidence of heart failure characterized by reduced left ventricular ejection fraction. (1) Sustained elevations in left atrial pressure cause pulmonary venous congestion which often leads to elevation of pulmonary pressures leading to severe right ventricular failure with a low cardiac output, edema, hypoxemia, and severely limited exercise capacity. (2) Pulmonary hypertension (PH) in subjects with heart failure and preserved ejection fraction (PH-HFpEF) is a common form of pulmonary hypertension and has an estimated US prevalence exceeding 1.5 million. (3)

PH-HFpEF has been classified within Group II of the WHO clinical classification of PH, characterized by PH arising from left heart disease. (4,5,6). Regardless of the basis of left heart disease, PH initially develops from a passive backward transmission of filling pressures, mainly driven by left ventricular (LV) diastolic function, resulting in a chronic increase in left atrial pressure and a loss of left atrial compliance. These mechanical components of pulmonary venous congestion may trigger pulmonary vasoconstriction, decreased nitric oxide (NO) availability, increased endothelin expression, desensitization to natriuretic peptide-induced vasodilation, and vascular remodeling. Finally, these changes often lead to advanced pulmonary vascular disease, increased right ventricle (RV) afterload, and RV failure. PH-HFpEF is defined hemodynamically by a pulmonary artery pressure (mPAP) ≥25 mmHg, a pulmonary capillary wedge pressure (PCWP) >15 mmHg, and a diastolic pressure gradient [diastolic PAP – PCWP] >7mmHg. (7)

In clinical trials of HFpEF, pharmacologic treatment has been largely neutral; only exercise training and weight loss appear to improve exercise intolerance and quality of life. (8) ESC guidelines in the treatment of PH-HFpEF subjects acknowledge that the accepted treatment target is a reduction of pulmonary wedge pressures using diuretics for congestion. However, clinical studies have demonstrated neutral results with identified concerns that PH-targeted therapies could have detrimental effects due to rapid increases in LV filling pressures, resulting in acute pulmonary edema. Thus, the ESC guidelines specify that there are currently no established strategies to treat pulmonary vascular disease (PVD) and right ventricular disease (RVD) in HFpEF, with a recommendation (class III) not to use approved PAH treatments in PH-HFpEF subjects. (4,9). With no demonstrated effective therapy, these subjects have a poor outcome (5 yr. survival <50%, frequent hospitalizations). (10)

1.2 Product Background

Levosimendan is a calcium sensitizer and potassium channel activator drug approved in over 60 countries for intravenous use in hospitalized subjects with acutely decompensated heart failure (ADHF). Approximately 1.5 million subjects have been treated with levosimendan worldwide by the end of December 2017.

A complete summary of the vast preclinical and clinical information in support of levosimendan' s pharmacological effects, efficacy and safety is included in the Levosimendan (Simdax) Investigator's Brochure (IB).

1.2.1 Preclinical Information

Levosimendan's activity is mediated through unique mechanisms of action, including:

- Increased cardiac contractility by calcium sensitization of troponin C. (11-14)
- Vasodilation through the opening of potassium channels. (15-18)
- Cardioprotective effects via potassium channel opening in mitochondria. (19-22)

Levosimendan has an active metabolite that extends its effects well beyond the infusion period. Following intravenous or oral dosing, levosimendan is reduced by intestinal bacteria to form OR-1855 (limited activity) that is acetylated to form OR-1896, an active metabolite. While the parent half-life is approximately 1 hour and cleared a few hours after the end of intravenous infusion, OR-1896 has a prolonged half-life of 70-80 hours in heart failure subjects with roughly equal exposures of OR-1855 and OR-1896 maintained through deacetylation/ acetylation pathways. The OR-1896 metabolite has been shown to retain similar hemodynamic and pharmacologic properties of levosimendan and maintain roughly equivalent effects to levosimendan in preclinical models. This activity occurs despite considerably lower plasma concentrations relative to levosimendan, an apparent result of a large percentage of unbound OR-1896 in circulation. (22-27). Thus, in extended repeated dosing, levosimendan is essentially an active prodrug to an active metabolite moiety, OR-1896.

Levosimendan has been shown to be a potent and selective phosphodiesterase-3 (PDE3) inhibitor *in vitro*. The drug is PDE3 selective with a PDE3/PDE4 inhibition ratio of 10,000. (15, 49). However, both isozymes must be inhibited in cardiomyocytes to exert an effect on the cAMP concentration and inotropic effects. The classical PDE inhibitors (i.e., milrinone, enoximone, and amrinone) inhibit both PDE3 and PDE4 at therapeutic concentrations (e.g., milrinone selectivity for PDE3 vs. PDE4 is as low as 17-fold), which accounts fully for their inotropic effect.

OR-1896 is equipotent to levosimendan in its inotropic effects in whole cardiomyocytes and isolated contractile apparatus preparations. However, OR-1896 is profoundly less potent in the inhibition of both PDE3 and PDE4 isozymes. This supports the hypothesis that the main component of the inotropic effect for both levosimendan and OR-1896 is a result of their binding to troponin C and not through PDE inhibition. (49)

1.2.2 Clinical Pharmacology

Clinical observations demonstrate that short-term levosimendan administration is followed by long-term hemodynamic changes that parallel the levels of OR-1896. (28) Thus, OR-1896 greatly extends the parent levosimendan's activity and provides the primary active moiety in subjects receiving intermittent intravenous levosimendan therapy.

Clinical studies have demonstrated therapeutic benefits to subjects with left ventricular dysfunction following acute doses and intermittent doses of levosimendan. These include:

1. Sustained therapeutic effects following a single 24-hr infusion of levosimendan in acute heart failure subjects:
   - Improved hemodynamics (29-31) without a significant increase in myocardial oxygen consumption. (32,33)
   - Reduced symptoms of acute heart failure. (29,30,34,35)
   - Beneficial effect on neurohormone levels. (34,35)
   - Sustained efficacy due to formation of an active metabolite (OR-1896). (36,37)
   - Additional benefit in subjects under beta-blockade. (29,38)

2. Sustained therapeutic effects of repeated intermittent infusions of levosimendan in chronic advanced heart failure subjects:
   - Beneficial effect on neurohormonal levels (39)
   - Reduced hospitalizations (39)

3. Demonstrated therapeutic effects of repeated 1-2mg daily oral doses of levosimendan in chronic advanced heart failure subjects including:
   - Beneficial effect on neurohormonal levels (40)
   - Improvement in QOL (40)
   - Successful weaning of continuous intravenous (IV) inotropes in inotrope dependent subjects. (41)

Levosimendan improves endothelial function and enhances diastolic coronary flow by opening the adenosine triphosphate-sensitive potassium channels (42) and increasing nitric oxide production (43). Levosimendan acts through direct binding to troponin-C at high systolic intracellular calcium concentration as well as detachment from it at low diastolic concentration are facilitated. Levosimendan displayed positive lusitropic effects relative to milrinone and nitroglycerin (44, 45). The lusitropic effect of levosimendan is independent of the degree of the inotropic effect.

1.2.3 Chronic Intermittent Studies of IV Levosimendan in Heart Failure and Pulmonary Hypertension Patients

The LEVO-REP, LION-HEART, and LAICA trials built on observations from earlier open-label studies that suggested benefits from levosimendan in this intermittent use. (45-47) These studies in subjects with heart failure and left ventricular dysfunction (LVEF <35%) investigated the effects of intermittent levosimendan at 0.2 µg/kg/min was administered for 6 h at 2-week intervals over 6 weeks or for 24 h every 4 weeks (46-48) These studies demonstrated improvements in NT-proBNP levels, subject quality of life, along with favorable reductions in hospitalizations and death.

Orion sponsored a placebo-controlled study of intermittent levosimendan in subjects with pulmonary hypertension (51). Patients included those with PAH (Group 1, n=8), pulmonary venous hypertension from LV failure (Group 2, n=17), and chronic thromboembolic disease

(Group 4, n=3). Levosimendan was administered 4 times at 2-week intervals as a continuous infusion of 0.2 μg/kg/min for 6 hours. Levosimendan treatment was associated with significant reductions in pulmonary vascular resistance (PVR) at 24 hours; mean increase of 12% ±9%, levosimendan; 25%±11% placebo group (p=0.009) The magnitude of the PVR response in levosimendan subjects was similar but not significant at eight weeks. Similar responses were observed in subject's mean pulmonary artery pressure (mPAP). Exercise capacity, pulmonary gas exchange, QOL, and days alive outside of the hospital were also improved on levosimendan but failed to reach significance. Seven out of 13 PH subjects with WHO-FC IV improved by one class (p=0.008). Borg dyspnoea scores, 6-MWD and NT-proBNP, improved significantly (p< 0.001). Compared with baseline, the right atrial transverse dimension, end-systolic eccentricity index and tricuspid annular plane systolic excursion improved significantly (58.8 ± 13.1 mm vs. 53.7 ± 12.4 mm; 1.50 ± 0.27 vs. 1.38 ± 0.23; 15.0 (13.0, 16.0) mm vs. 15.8 (14.0, 17.4) mm, p< 0.005, respectively).

1.2.4 Levosimendan Clinical Safety

The primary safety events of interest in levosimendan administration are hypotension and tachycardia.

In integrated safety data in heart failure subjects from placebo-controlled IV levosimendan studies, there are no differences in the frequencies of decreased BP in levosimendan treated subjects compared to placebo-treated subjects (23.1% vs. 23.1%). However, in the largest placebo-controlled trial with IV levosimendan (REVIVE II) a statistically significantly greater proportion of levosimendan-treated subjects experienced decrease in BP (52.6%) compared to the placebo group (37.9%), p < 0.001. This study employed a high bolus dose, then titration after 1 hour to 0.2 μg/kg/min for 23 hours.

In the integrated data of placebo-controlled IV levosimendan studies, atrial tachycardia and fibrillation are seen in 8.2% in the levosimendan group compared to 5.4% in the placebo group (p = 0.024). This difference was also seen in REVIVE II (9% vs. 2%, p < 0.001). In REVIVE II, a statistically significant difference in the incidences of ventricular tachycardia could also be seen (25% in the levosimendan group and 17% in the placebo group, p = 0.031). However, in the integrated data, the events in the grouping of 'ventricular tachycardia and fibrillation' are reported in 10.0% of the levosimendan treated subjects and in 11.3% of the placebo subjects (p = 0. 371).

The incidences of worsening heart failure (15.6% vs. 28.4%, p < 0.001) and renal function disturbances (6.9% vs. 10.4%, p = 0.007) are significantly lower in the levosimendan group than in the placebo group.

No statistically significant difference in cardiac ischemia (7.3% vs. 8.9%, p = 0.233), decreased hemoglobin (2.3% vs. 3.8%, p = 0.058), decreased potassium (4.9% vs. 7.0%, p = 0.059) or increased blood glucose (1.6% vs. 2.6%, p = 0.117) are seen between levosimendan and placebo groups. It is noteworthy that although no statistically significant differences in the frequency of decreased hemoglobin and decreased potassium are seen, the numerical differences favor

levosimendan. This contrasts with the laboratory safety variable analyses; in IV studies decreases in hemoglobin and serum potassium have been consistently reported (29, 47).

In pulmonary hypertension subjects eleven (61%) of levosimendan-treated subjects experienced at least one AE compared with 8 (80%) of placebo-treated subjects (51). The majority were mild to moderate; no statistically significant differences were observed in any AE. The most commonly observed AEs in PH subjects were hypotension and headache, paralleling the most common AEs observed in HF subjects. Four levosimendan subjects experienced eight hypotensive events. Two of the hypotensive events were symptomatic and experienced during the initial 24-hour infusion at 0.1 titrated to 0.2 μg/kg/min with a mean duration of 12 hours. The other six asymptomatic hypotension events had a mean duration of 3.2 hours. Five dose-limiting hypotensive events occurred in three levosimendan subjects.

One levosimendan subject discontinued the study prematurely because of prolonged hypotension, which started 20 minutes after completing the 24-hour infusion. One subject experienced severe hypotension at the conclusion of their 24hr levosimendan dose. Greater increases in HR and decreases in blood pressure were observed in levosimendan-treated subjects during the initial 24-hour infusion. However, the HR and blood pressure responses during the subsequent 6-hour infusions were similar between groups.

In marketed use, approximately 1.5 million subjects worldwide have been treated with Simdax® (levosimendan) injection. The most commonly reported adverse reactions in the adverse drug reaction reports received from healthcare professionals, consumers, regulatory authorities, clinical studies and observed in the worldwide literature are hypotension, ventricular tachycardia, cardiac failure and ventricular fibrillation. These events are included in the Simdax (levosimendan) EU Summary of Product Characteristics (SPC) (see Investigator's Brochure for a copy of the SPC).

1.2.5 Rationale for Chronic Intermittent (weekly) Levosimendan for PH-HFpEF Patients

The use of intravenous levosimendan in the treatment of PH-HFpEF subjects is based on the following.

- Levosimendan uniquely enhances myocardial activity through a tripartite mechanism which involves acting as a calcium sensitizer in cardiomyocytes by increasing the sensitivity of troponin C fibers to ionic calcium and as a vasodilator and cytoprotective agent through the opening of adenosine triphosphate (ATP)-dependent potassium channels on vascular smooth muscle cells and in mitochondria.
- Levosimendan enhances CO and systolic and diastolic function, promotes vasodilatation and peripheral perfusion, reduces pulmonary capillary wedge pressure (PCWP), alleviates symptoms of dyspnea and fatigue, and reduces levels of signifier neurohormones such as brain natriuretic peptide (BNP).
- Preliminary clinical studies with levosimendan in subjects with right heart failure and pulmonary hypertension suggest the drug will lower pulmonary vascular resistance in PH-HFpEF subjects.
- The data on the hemodynamic effects of levosimendan in the clinical studies of patients with LV failure consistently demonstrate that levosimendan will lower

PCWP, lower PA pressure, and increase cardiac output which is the desired effect of a treatment for PH-HFpEF.

- Levosimendan clinical data in chronic intermittent dosing support a regimen of 0.10µg/kg levosimendan for 24 hrs, followed by weekly levosimendan infusions of 0.075µg/kg/min for 24 hrs (or 0.10µg/kg/min for 24 hrs in subjects that have not responded adequately to weekly therapy) should be safe and well-tolerated and maintain effective levels of the active metabolite OR-1896 in PH-HFpEF subjects.

1.2.6 Target Plasma Concentrations of OR-1896 in intermittent treatment of PH-HFpEF Patients

Levosimendan represents an active prodrug to the active metabolite OR-1896 with extended pharmacodynamic (PD) effects that parallel those of levosimendan. The elimination half-life of levosimendan itself is short (approximately 1 hour), whereas that of the metabolite OR-1896 is long (70-80 hours in heart failure subjects). During a long-term oral dosing of levosimendan with constant daily dose, the OR-1896 plasma levels achieve a steady-state with minimal daily variation.

The PERSIST Study of daily oral levosimendan doses of 1 and 2 mg for 180 days or more demonstrated substantial reductions in NT-proBNP and dose-related improvement in the Minnesota Living with Heart Failure quality of life score (MLHFQOL). Thus, the observed levosimendan low dose with steady state OR-1896 concentrations of ~2.5ng/mL was associated with robust efficacy in HF subjects.

Extended studies of IV levosimendan in HF subjects suggest a lower steady state concentration of OR-1896 may be efficacious. The LEVO- REP and LION HEART studies of levosimendan in severe heart failure subjects (NYHA III/IV) were dosed at 0.2µg/kg/min infusions for 6 hrs. every two weeks for 6 weeks and 12 weeks, respectively. Levosimendan-treated subjects had reductions in NT-pro-BNP and increased exercise capacity with enhanced quality of life (QOL). Steady state concentrations of OR-1896 were not determined in these studies of repetitive IV levosimendan.

OR-1896 concentrations were modeled for the intravenous levosimendan dose regimen used in LEVO-REP and LION-HEART (0.2µg/kg/min for 6 hrs. every two weeks). OR-1896 concentrations displayed average Cmax and Cmin values of 1.5 ng/mL and 0.25 ng/mL, respectively, with a Cavg of approximately 1.0 ng/mL during each two-week dose interval. The effective target concentrations of OR-1896 are expected to be between 0.5 ng/mL and 2.5 ng/mL in extended intermittent use.

Full population PK simulations of OR-1896 plasma levels have been performed using available PK data of levosimendan, OR-1855, and OR-1896 from studies of IV and oral doses of levosimendan in heart failure subjects. Simulations were based on central and peripheral compartment for levosimendan, central compartments for OR-1855 and OR-1896, and two transit compartments for levosimendan metabolizing to OR-1855.

Covariates included the following:

- Acetylation status for metabolism from OR-1855 to OR-1896, and vice versa
- Weight and sex on levosimendan central compartment volume of distribution
- Age on levosimendan intercompartmental clearance

These simulations supported an intravenous levosimendan initial dose of 0.10µg/kg/min for 24 hours, followed by weekly doses of 0.075µg/kg/min for 24 hours through Week 3 and, 0.10 µg/kg/min for 24 hours through Week 5. This intravenous levosimendan regimen should provide effective OR-1896 concentrations between approximately 0.5 ng/mL and 2.5 ng/mL at half the rate of infusion used in LEVO-REP and LION-HEART, and the completed study in pulmonary hypertension subjects (Orion Study 3001064).

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

The study will evaluate the efficacy and safety of intermittent levosimendan compared with placebo in hemodynamic improvement with exercise in PH-HFpEF subjects. This subject population represents a large and growing group with no established therapies to treat their pulmonary vascular disease (PVD) and right ventricular disease (RVD). Levosimendan and its prolonged active metabolite, OR-1896, have been shown to have favorable hemodynamic effects in subjects with pulmonary hypertension and right heart failure. Clinical studies that have been conducted in subjects with right heart failure and pulmonary hypertension suggest levosimendan may be an effective therapy in treatment of subjects with PH-HFpEF.

This study will provide demonstration of levosimendan/OR-1896's effectiveness in critical measures of hemodynamic response in weekly administration of levosimendan and the concomitant response as measured by exercise capacity, subject quality of life, and changes in functional capacity. These data will support and guide the Phase 3 development of levosimendan in PH-HFpEF subjects.

2.2 Study Objectives

2.2.1 Primary Objectives

This study will evaluate the efficacy and safety of intermittent (weekly) levosimendan infusions in hemodynamic improvement with exercise in PH-HFpEF subjects.

2.2.2 Secondary Objectives

The study will evaluate the effectiveness of intermittent (weekly) levosimendan infusions in improving the following:

- Change in Cardiac Index at rest and with exercise at Week 6
- Change in PVR effect at rest and with exercise at Week 6
- Change in PCWP when supine and legs elevated at Week 6
- Patient global assessment (based on a six-point Likert scale) at Week 6
- Exercise duration 6-min walk test at Week 6
- Physician's Assessment of Functional Class
- Clinical Events: Death and hospitalizations
    - All cause hospitalizations
    - Hospitalizations attributed to any abnormality in cardiac and/or pulmonary status.

2.2.3 Exploratory Objectives

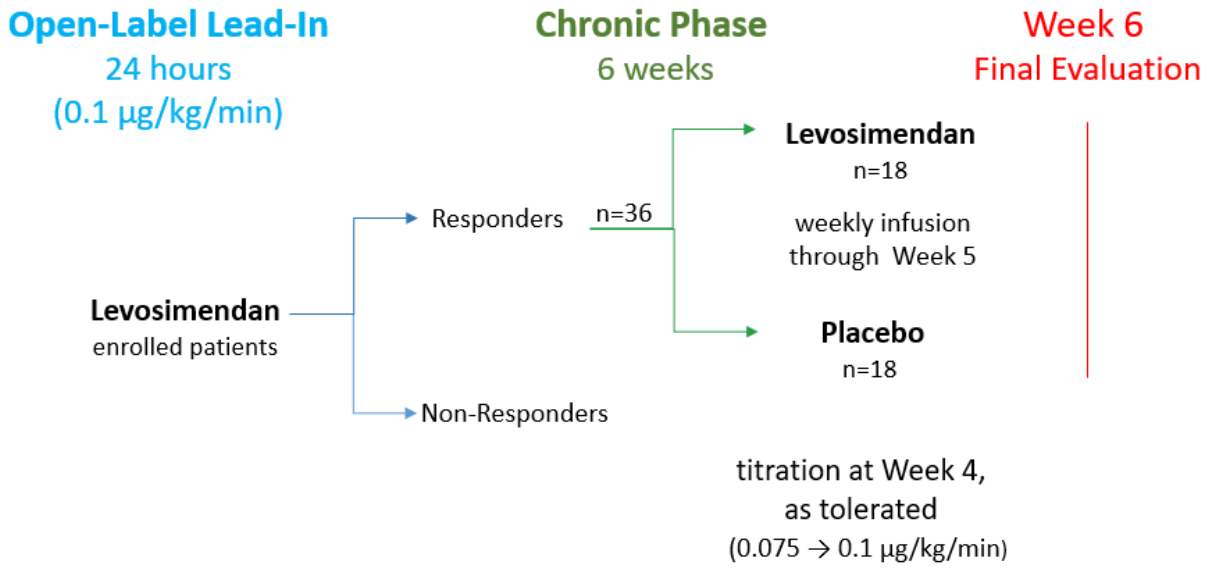
Baseline echocardiographic measurements of RV and LV function to predict favorable response to levosimendan therapy.

3. STUDY DESIGN

3.1 Study Design

The Phase 2 study of levosimendan in PH-HFpEF subjects has been designed in two phases (Figure 1). The lead-in phase will evaluate qualifying subject's acute hemodynamic response to open-label levosimendan. Patients that have clinically relevant responses to levosimendan will be randomized to levosimendan or placebo (1:1) and receive intermittent (weekly) study drug infusions (Week 2-5). Patients who do not tolerate the initial levosimendan infusion due to excessive hypotension or tachycardia will be dropped from eligibility. Patients will be evaluated Week 6 to determine the efficacy and safety of levosimendan.

Figure 1: Study Design Flow Chart



3.2 Number and Type of Subjects

The study will recruit male and female subjects meeting identified enrollment criteria for PH-HFpEF into the lead-in open label phase to identify "responders" to levosimendan intravenous infusion of at 0.10 µg/kg/min for 24 hours ±30 min. Subjects that have clinically relevant responses to levosimendan will be randomized to levosimendan or placebo (1:1) and receive intermittent (weekly) study drug infusions (Week 2-5). The first 36 subjects who demonstrate a ≥4mmHg reduction in PCWP from baseline measured at bicycle exercise (25 watts) with no more than a 10% decrease from baseline in cardiac index will be classified as a "responder" to the lead-in levosimendan dose and be randomized to the double-blind phase of the study. Randomized subjects that have not received study drug weekly through Week 5 and returned for evaluation on Week 6 will be replaced to ensure 18 subjects have completed in each study group.

3.3 Investigational Product

Levosimendan, or matching placebo supplied as a concentrated solution (2.5 mg/mL). Levosimendan will be administered in open-label lead-in dose intravenously at 0.10 µg/kg/min for 24 hours ±30 min. Patients responding to the lead-in levosimendan dose will be randomized to levosimendan or placebo and receive a weekly dose of study drug intravenously at 0.075 µg/kg/min for 24 hours ±30 min and if tolerated titrated to 0.10 µg/kg/min for 24 hours ±30 min at Week 4.

3.4 Sites and Regions

This study will be conducted at approximately 20-25 sites in the United States.

4. STUDY POPULATION

4.1 Inclusion Criteria

Diagnosis and main criteria for inclusion and exclusion:

Patients must meet the following criteria to be enrolled in the study:

Enrollment Criteria:

1. Men or women, ≥18 years of age
2. Diagnosis of WHO Group 2 Pulmonary Hypertension (PH) with heart failure and preserved ejection fraction (HFpEF) confirmed at the time of the diagnosis of pulmonary hypertension (see Attachment 2).
3. Pulmonary Hypertension subjects with heart failure and preserved ejection fraction as defined by:
    a. Mean pulmonary arterial pressure (mPAP) ≥ 35 mmHg at rest or with legs up (at baseline right heart catheter, Lead-In)
    b. Pulmonary capillary wedge pressure ≥20 mmHg at rest or with legs up (at baseline right heart catheter, Lead-In)
    c. NYHA Class II or III
    d. LVEF ≥40% by echocardiogram within three months of enrollment
4. Signed (by the subjects or their legally acceptable representatives) informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.
5. Ability to walk at least 50 meters, but not more than 550 meters in a six-minute walk test.
6. Long term oxygen treatment (if applicable) must be stable for 30 days prior to enrollment.

7. Subjects on a chronic medication or therapy for any underlying cardiac condition must be on a stable dose for ≥30 days prior to randomization, with the exception of diuretics and antihypertensive medication for blood pressure control which may be discontinued if deemed appropriate.

8. Subjects on chronic medications for any underlying respiratory condition must be on a stable dose for ≥30 days prior to randomization

Note: With regard to Inclusion Criteria 6-8, "stable" refers to changes in oxygenation therapy or medications no greater than a 100% increase or a 50% decrease, as needed to optimize the patient.

Randomization Criterion:

9. Response to Open-Label Levosimendan: Patients who demonstrate a ≥4mmHg reduction in PCWP from baseline measured during bicycle exercise (25 watts) with no more than a 10% decrease from baseline in cardiac index with no clinically excessive hypotension or tachycardia (see Attachment 5).

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met.

1. Previous PCI or cardiac surgery (CABG) unless documented to have negative stress test within the last 12 months
2. Clinically symptomatic mitral or aortic valvular heart disease.
3. Cardiac index greater than 4.0 L/min/m^2
4. In the opinion of the Principal Investigator, the subject has a primary diagnosis of PH other than WHO Group 2 PH-HFpEF
5. Congenital heart disease other than surgically corrected pre and post tricuspid shunts for at least 10 years
6. Symptomatic coronary artery disease based on positive stress test
7. Patients planning lung or heart transplant or cardiac surgery in the next 4 months

8. Patients diagnosed with pulmonary hypertension associated with clinically significant lung disease at the time of initial diagnosis, or patients with a congenital defect of the lung
    a. Clinically significant obstructive lung disease is defined as FEV1/FVC <60% of predicted, unless a high resolution chest CT scan shows no more than mild areas of emphysematous changes.
    b. Clinically significant restrictive lung disease is defined as disease a FVC of <60% of predicted, unless a high resolution chest CT scan shows no more than mild areas of interstitial lung disease or pulmonary fibrosis.
9. Dialysis at randomization (either hemodialysis, peritoneal dialysis, continuous venovenous hemofiltration, or ultrafiltration)
10. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2
11. Liver dysfunction with Child Pugh Class B or C (see Attachment 3)
12. Evidence of systemic bacterial, systemic fungal, or viral infection in last 2 weeks
13. Weight >150 kg
14. Symptomatic low systolic blood pressure (SBP) that cannot be managed to ensure SBP $\geq$ 100 mmHg at initiation of study drug
15. Heart rate ≥ 100 bpm with study drug, symptomatic and persistent for at least 10 minutes at screening.
16. Hemoglobin < 80 g/L
17. Serum potassium < 3.0 mmol/L or > 5.5 mmol/L at baseline
18. Pregnant, suspected to be pregnant, or breast-feeding
19. Known allergic reaction or sensitivity to levosimendan or excipients.
20. A history of Torsades de Pointes
21. Received levosimendan within 30 days before the planned start of study drug
22. Received an experimental drug or used an experimental medical device within 30 days before the planned start of study drug
23. Concomitant administration of pulmonary vasodilator therapy, or taken within 14 days of randomization

24. Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator
25. Inability to comply with planned study procedures

4.3 Restrictions

Potential subjects must be willing to adhere to the following prohibitions and restrictions during the study to be eligible for participation.

- Women of childbearing potential only must agree to remain on an effective method of birth control or remain abstinent throughout the study.
- Medication or treatment for heart failure or respiratory disease must be maintained during the trial, unless contraindicated
- All subjects must agree and comply with at-home infusions for the duration of the trial.

4.4 Withdrawal of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The Investigator or Sponsor may withdraw the subject at any time (e.g., in the interest of subject safety). The withdrawal of a subject from the investigational product by the Investigator should be discussed where possible with the Medical Monitor and/or Sponsor before the subject stops investigational product.

If the investigational product is discontinued, regardless of the reason, the final evaluations are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified Week 6 evaluations. Comments (spontaneous or elicited) made by the subject must be recorded in the source documents. The reason for termination, date of stopping investigational product, and the total amount of investigational product taken must be recorded on the electronic Case Report Form (eCRF) and source documents.

4.4.1 Reasons for Discontinuation

The reason for withdrawal must be determined by the Investigator and recorded in the subject's medical record and on the eCRF. If a subject is withdrawn for more than one reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the eCRF.

If an adverse event (AE) is a reason for discontinuation, then "Adverse event" must be recorded as the reason for discontinuation on the eCRF.

Reasons for discontinuation include but are not limited to:

- Adverse event
- Protocol violation
- Withdrawal by subject
- Lost to follow-up
- Lack of efficacy
- Investigator decision

4.4.2 Subjects 'Lost to Follow-up' Prior to Last Scheduled Visit

At least three documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). One of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgment of receipt request) asking that they return any unused investigational product (if applicable) and return to the site for final safety evaluations.

5. PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Treatment

Prior treatment includes all treatment (including herbal treatments, vitamins, nonpharmacological treatment such as psychotherapy as appropriate) received within 30 days (or the pharmacokinetic equivalent of 5 half-lives, whichever is longer) of and discontinued prior to the date of the first dose of investigational product. Prior treatment information must be recorded on the appropriate eCRF page.

5.2 Concomitant Treatment

All subjects must be optimally managed on diuretics and oxygen therapy as indicated by the standard of care. Diuretic dose may not be adjusted within 5 days of Levosimendan infusion.

Concomitant administration of parenteral prostacyclin is not permitted.

The long-term oxygen treatment (if applicable) must be stable for 30 days prior to enrollment, including delivery route and dose.

Medication or treatment for heart failure or respiratory disease must be maintained during the trial, unless contraindicated.

6. RANDOMIZATION

Randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during treatment, data collection and evaluation of clinical endpoints.

Subjects will be randomly assigned to a treatment group using an interactive web response system (IWRS) after they have met all inclusion criteria and none of the exclusion criteria.

If a potential subject is randomly assigned to treatment but is found to be ineligible before the study drug infusion is started, the investigator will not proceed with study drug administration. The potential subject will be considered randomized but not treated, and the sponsor must be notified. The investigator will document the reason that the potential subject is no longer a study candidate within the eCRF.

Once a randomization number/unique identifier has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. If a randomization number/unique identifier is allocated incorrectly the sponsor must be notified as soon as the error is discovered.

6.1 Allocation of Subjects to Treatment

This is a double-blind, placebo/active-controlled study. The actual treatment given to individual subjects is determined by the randomization schedule.

Subject screening numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), this number is assigned to subjects according to the sequence of presentation for study participation.

Upon randomization, subjects will be assigned to 1 of 2 treatment groups (levosimendan 0.075 µg/kg/min for 24 hours (±30 min) or matching placebo) in a 1:1 ratio based on a computer-generated randomization schedule.

Lead-in Phase (Day 0)
Levosimendan will be administered to all subjects meeting inclusion criteria into the study to assess clinically relevant response to levosimendan. The dose is 0.1 µg/kg/min for 24 hours (±30 min).

Double-blind Phase (Weeks 2, 3, 4, 5, and 6)
Study drug levosimendan or placebo (1:1 randomization), will be administered at study Weeks 2, 3, 4 and 5 via a CADD pump and initiated by the home healthcare nurse.

During Weeks 2 and 3, patients will receive levosimendan or placebo at a rate of 0.075 µg/kg/min for 24 hrs.

Patients will have a dose escalation at Weeks 4 and 5 at a rate of 0.10 µg/kg/min for 24 hrs unless there has been a meaningful change in blood pressure or heart rate (Attachment 5).

After the completion of all Week 6 procedures, randomized subjects will be offered the option to enroll into an open-label study of levosimendan. Subjects will be required to sign a new informed consent form to enroll in this open-label trial.

7. INVESTIGATIONAL PRODUCT

7.1 Levosimendan

Levosimendan and matching placebo will be provided to investigators by the sponsor as a sterile clear, yellow to orange solution in clear glass vials. Each vial contains a 5 mL volume and is intended for a single use. Levosimendan is supplied at 2.5 mg/mL (12.5 mg/5 mL) and includes levosimendan, povidone, citric acid and ethanol. Additional information is provided in the Simdax (levosimendan) injection Investigator's Brochure and SmPC.

Levosimendan and matching placebo are manufactured by the Orion Corporation, Espoo, Finland.

7.2 Matching Placebo

Placebo is a sterile infusion solution that includes a coloring agent in order to achieve a similar color to levosimendan. The complete composition of placebo for levosimendan 2.5 mg/mL infusion concentrate includes riboflavin sodium phosphate, ethanol, and water for injection.

7.3 Packaging

Levosimendan and placebo will be provided in sterile, single-use clear rubber-stoppered glass vials. Details on the packaging of study drug will be provided in the study manual.

Initially, investigational sites will receive single vials of levosimendan to complete the Lead-In dose for approximately 6 patients. For subsequent dosing at Weeks 2 through 5, kits will be labeled (levosimendan and matching placebo) and will include 2 vials per kit to ensure sufficient supply is available for patients over 85kg in weight.

7.4 Labeling

Study drug labels and cartons will contain information to meet the applicable regulatory requirements.

Each vial will have appropriate directions for use and other information on each part.

Specialized drug accountability forms will be provided for tracking study drug administration. Information from the vial will be included on the subject's drug accountability form to document drug reconstitution (vial usage). See the Pharmacy Manual for detailed instructions.

7.5 Preparation and Handling

Study drug (levosimendan, placebo) will be prepared by study personnel blinded to the treatment group.

Levosimendan 2.5 mg/mL (Simdax, Orion Corporation, Espoo, Finland) infusion concentrate is supplied in a volume of 5 mL (with a small overage) in clear rubber-stoppered glass vials. The composition of levosimendan 2.5 mg/mL infusion concentrates includes Levosimendan, povidone, citric acid, and ethanol.

Study drug (levosimendan infusion concentrate, placebo concentrate) must be stored between 2-8°C (35-46°F) in a temperature monitored refrigerator which can be locked and protected from light.

The study drug should be prepared immediately prior to use. Dilution of the study drug should be performed as described below.

One (or two) 5 mL vials of study drug (from one of the two subject pack boxes in a numbered package) are added to one 250 mL (or 500 mL) infusion bag of 5% Dextrose or 0.9 Normal Saline according to the subject's body weight as follows.

- For subjects < 85 kg by adding one (1) 5 mL vial of levosimendan/placebo infusion concentrate to one 250 mL infusion bag or bottle of 5% Dextrose or 0.9 Normal Saline.

- For subjects ≥ 85 kg by adding two (2) 5 mL vials of levosimendan/placebo infusion concentrate to one 500 mL infusion bag or bottle of 5% Dextrose or 0.9 Normal Saline.

The concentration of the study drug is approximately 50 μg/mL (12.5 mg/255 mL in a 250 mL bag; 25 mg/510 mL in a 500 mL bag). Immediately after dilution, the infusion bags are covered with IV/tubing sleeves to protect the infusion solution from light. Label information found on each vial is completed by the study nurse and then transferred to the infusion bag to confirm dilution. Empty vials must not be discarded but placed back in the box and stored for reconciliation.

Since the stability of the diluted medication has been established for 30 hours only, the study drug infusion must not continue for more than 30 hours after the time of initial dilution. On completion of the 24-hour infusion period, all study medication bags (and contents) still covered by the amber sleeve should be destroyed appropriately and destruction will be documented. The colored plastic sleeves must not be removed or tampered with by the study center team members.

7.5.1 Lead-in and Double-blind

Lead-in Phase
Levosimendan, supplied as a concentrated solution (2.5 mg/mL), will be mixed with diluent and administered intravenously at 0.10 µg/kg/min for 24 hours ±30 min.

Double-blind Phase
Study drug concentrated solution (2.5 mg/mL), levosimendan or placebo, will be mixed with diluent and administered via a PICC line as weekly infusions at 0.075 µg/kg/min for 24 hrs. Patients will have a dose escalation at Weeks 4 and 5 at a rate of 0.10 µg/kg/min for 24 hrs, unless there has been a meaningful change in blood pressure or heart rate (Attachment 5).

Infusion rates may be reduced to 0.05 µg/kg/min if the higher dose is not well-tolerated at any time during the study (see Attachment 1).

Infusions should typically occur as follows, unless there is the need for adjustment:

Lead-In Infusion (in office)	Week 2 (Home)	Week 3 (Home)	Week 4 (Home)	Week 5 (Home)	Week 6 (in office)
0.10 µg/kg/min for 24 hrs	0.075 µg/kg/min for 24 hrs	0.075 µg/kg/min for 24 hrs	0.10 µg/kg/min for 24 hrs	0.10 µg/kg/min for 24 hrs	Discontinuation or Enrollment into OL

Prior to the Week 4 infusion, subjects will be assessed by the investigator per section 8.5.

7.5.2 Dosage and Administration

Prior to initiating study drug infusion, subjects should be checked for (mean arterial pressure [MAP] < 60 mmHg, SBP < 100 mmHg). Confirm the subject has not modified their diuretic dose in the last 5 days.

During the Lead-In Phase, subjects will be administered a continuous intravenous (IV) infusion of a standard infusion dose of 0.10 µg/kg/min for 24 hours (±30 min); (levosimendan). No bolus of study drug will be administered.

The infusion rate of study drug may be decreased, interrupted, or discontinued for safety reasons, according to the discretion of the investigator, as described in the following sections.

To prevent possible medication errors or miscalculations, refer to Attachment 1 of this protocol before administration of study drug to calculate the appropriate infusion rate based on the subject's preoperative body weight.

See Section 7.5, Preparation and Handling for information on study drug preparation.

The diluted infusion is administered intravenously by a peripheral or central route. No other treatments should be administered via the same line. The concentration of the diluted infusion

is about 50 µg/mL in 5% Dextrose or 0.9% Normal Saline (12.5mg/255mL in a 250 mL bag; 25mg/510mL, 2 vials in a 500 mL bag).

The IV tubing should be primed to fill the volume to the IV entry site before starting the infusion.

Patients will receive the infusion via a CADD pump. Patients will be allowed to resume their normal daily activity during the infusion but will not be allowed to engage in any activity that may subject the CADD pump to water exposure.

7.5.3 Dose Adjustment

The infusion rate of study drug may be decreased or interrupted as clinically warranted if the subject has hypotension, tachycardia, or signs or symptoms consistent with hypovolemia (e.g., low SBP, decreasing urine output with rising blood urea nitrogen [BUN] and serum creatinine) Record the time of discontinuation or down titration. Patients should be monitored closely until clinically stable. See Attachment 1 for infusion rates and instructions on dose adjustments.

Refer to the following subsections for additional guidance on events that require study drug discontinuation or dosage adjustment, permanent discontinuation, and re-initiating study drug in subjects in whom clinical stability has been restored. In the event of a dose interruption, the infusion should be extended the amount of time of the interruption, but no more than four hours.

7.5.4 Dose-limiting Events

Dose limiting cardiac events and instructions are detailed in Attachment 5. In addition to these events, the dose may be adjusted at any time the physician judges that it is in the best interest of the patient to reduce the dose or discontinue the infusion.

7.5.5 Blinding the Treatment Assignment

The blind is maintained by the use of matching placebo.

Protective sheaths for the infusion line and bag will be used to protect the study drug from UV light and are required to be used at Lead-In and during the Week 2 through 5 infusion visits.

Under normal circumstances, the blind should not be broken until all subjects have completed the study (defined as Week 6) and the database is locked. Otherwise, the blind should be broken only if specific emergency treatment would be dictated by knowing the treatment status of the subject. In such cases, the investigator must contact the sponsor or designee. Please consult the Pharmacy Manual for unblinding procedures should the sponsor or designee be unavailable. The sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in the appropriate section of the eCRF and in the source document.

7.5.6 Unblinding the Treatment Assignment

Data that may potentially unblind the treatment assignment (e.g., investigational product serum concentrations, antibodies to investigational product, treatment allocation, and investigational product preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

The treatment assignment must not be broken during the study except in emergency situations where the identification of the investigational product is required for further treatment of the subject. Prior to unblinding, and if the situation allows it, the investigator should first contact the Medpace Medical Monitor.

In the event that the treatment assignment is broken, the date, the signature of the person who broke the code, and the reason for breaking the code are recorded in the IWRS, eCRF, and the source documents (as appropriate). Upon breaking the blind, the subject is withdrawn from the study, but should be followed up for safety purposes. Any code-breaks that occur must be reported to the Sponsor. Instructions on breaking the blind for safety purposes are in the Pharmacy Manual.

7.6 Packaging, Storage, and Handling

7.6.1 Preparation and Handling

Study drug (levosimendan, placebo) will be prepared by study personnel blinded to the treatment group.

Levosimendan 2.5 mg/mL (Simdax, Orion Corporation, Espoo, Finland) infusion concentrate is supplied in a volume of 5 mL (with a small overage) in clear rubber-stoppered glass vials. The composition of levosimendan 2.5 mg/mL infusion concentrates includes: Levosimendan, povidone, citric acid and ethanol.

The study drug should be prepared no more than 6 hours prior to the initiation of an infusion. Dilution of the study drug should be performed as described below.

One (or two) 5 mL vials of study drug (from one of the two subject pack boxes in a numbered package) are added to one 250 mL (or 500 mL) infusion bag of 5% Dextrose or 0.9 Normal Saline according to the subject's body weight as follows.

- For subjects < 85 kg by adding one (1) 5 mL vial of levosimendan/placebo infusion concentrate to one 250 mL infusion bag or bottle of 5% Dextrose or 0.9 Normal Saline.

- For subjects ≥ 85 kg by adding two (2) 5 mL vials of levosimendan/placebo infusion concentrate to one 500 mL infusion bag or bottle of 5% Dextrose or 0.9 Normal Saline.

The concentration of the study drug is approximately 50 μg/mL (12.5 mg/255 mL in a 250 mL bag; 25 mg/510 mL in a 500 mL bag). Immediately after dilution, the infusion bags are covered with IV/tubing sleeves to protect the infusion solution from light. The label found on each vial is completed by the study nurse and then label information transferred to the infusion bag to confirm dilution. Information from the label is transferred by the investigator (study nurse) on starting the infusion and included on the drug accountability documentation. The eCRF will be updated to confirm the study drug received by an individual subject. Empty vials must not be discarded but placed back in the box and stored for reconciliation.

Since the stability of the diluted medication has been established for 30 hours only, the study drug infusion must not continue for more than 30 hours after the time of initial dilution. On completion of the 24-hour infusion period, all study medication bags (and contents) still covered by the amber sleeve should be destroyed appropriately, and destruction documented. The colored plastic sleeves must not be removed during infusion.

7.6.2 Storage

Study drug (levosimendan infusion concentrate, placebo concentrate) must be stored between 2-8°C (35-46°F) in a temperature monitored refrigerator which can be locked and protected from light.

The Sponsor must be notified upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. Tenax will determine the ultimate impact of excursions on the investigational product and will provide supporting documentation as necessary. Under no circumstances should product be dispensed to subjects until the impact is determined and product is deemed appropriate for use.

7.7 Investigational Product Quality Complaints

Investigators are required to report investigational product quality complaints to Tenax. This includes any instances wherein the quality or performance of a Tenax product does not meet expectations (e.g., inadequate or faulty closure, product contamination, etc.).

7.8 Drug Accountability

Investigators will be provided with sufficient amounts of levosimendan for the lead-in phase for the agreed number of subjects. The Investigator or designee will acknowledge receipt of the investigational product documenting shipment content and condition. The central depot for the home health services company will be provided with blinded drug supplies for doses at Weeks 2-5 and open-label levosimendan for the open-label extension. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The Investigator or his/her designee (as documented by the Investigator in the applicable study delegation of authority form) and home health care nurse will administer the investigational

product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All dispensing will be documented on the eCRFs and/or other investigational product record. The Investigator and home health care nurse is responsible for assuring the retrieval of all study supplies from subjects during lead-in and double-blind phases of the study. During the open-label extension, the home health care nurse must request subjects to keep the empty investigational product packaging after use and return it to the site for drug accountability purposes.

No investigational product stock or returned inventory from a Tenax sponsored study may be removed from a site where originally shipped without prior knowledge and consent by the Sponsor. If such transfer is authorized, all applicable local, state, and national laws must be adhered to for the transfer.

Tenax or its representatives must be permitted access to review the supplies storage and distribution procedures and records provided that the blind of the study is not compromised.

With the written agreement of Tenax, at the end of the study all unused stock, subject returned investigational product, and empty/used investigational product packaging may be destroyed at the site or a local facility. In this case, destruction records identifying what was destroyed, when and how must be obtained with copies provided to Tenax. Destruction of investigational products must be in accordance with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to Tenax' satisfaction.

7.9 Subject Compliance

Study drug will be administered as an IV infusion by qualified staff (e.g., a qualified nurse, a member of the study staff, or an infusion specialist) and the details of each administration will be recorded in the eCRF (including start and stop date and times of the IV infusion). The investigator or designated study personnel will maintain a log of all study drug dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study. b

8. STUDY PROCEDURES

The Time and Events Schedule summarizes the frequency and timing of efficacy, safety, or other measurements.

The study will be divided into a Screening phase, a Lead-In phase, and a Double-Blind treatment phase. Randomized and treated subjects will be followed for 6 weeks. At the end of 6 weeks, subjects will have the opportunity to continue receiving open-label levosimendan as long as they meet the criteria listed in section 8.6.2.

The Screening, Lead-In, Interim Office (between Weeks 3 and 4) and Week 6 visits will occur at the investigator's office. Infusions at Weeks 2, 3, 4 and 5 will occur at the subject's home under the care of a home healthcare nurse. Subjects will be instructed to contact the investigator at any time during the 24 hour at home infusions to report adverse events, or at any time they would like to speak with the investigator regarding the study or to report adverse events during the entirety of the trial. During the at home care, any urgent issues related to the infusion or the infusion pump should be directed to the 24-hour Coram Pharmacy hotline.

Visits during the Lead-In phase of the trial will require a subject to be hospitalized for the entire infusion period, which at a minimum will last 24 hours. Once the infusion is complete, hemodynamic measurements will be collected to ensure subject eligibility.

Visits for Week 2 through Week 6 should be calculated based on the date of the Lead-in infusion (not the date of randomization).

After confirmation of eligibility, patients will receive a blood pressure monitor for home use. Patients will be instructed to use the monitor if they notice any signs or symptoms of lightheadedness, dizziness, angina, or palpitations. The patients will also be instructed to contact the investigational site (24-hour medical hotline) to report any of these events or any adverse events. Patients should continue to use the monitor, as needed, post Lead-in infusion (Day 0) through the Week 6 visit.

8.1 Screening Visit (≤ 28 Days prior to Day 0)

Before any study-related procedures are performed, the risks of the study will be explained to a potential subject, and the subject or his/her legal representative will be required to sign an informed consent form.

In the Screening phase, which can occur over twenty-eight days, potential subjects will be screened to determine eligibility for participation in the study. Documentation of screening failure details should be recorded in the eCRF.

At least 72 hours prior to the first infusion (Lead-In Visit), all patients will wear a small, lightweight cardiac monitoring sensor on their chest to measure heart rate and to detect any arrhythmias. This patch will remain on monitoring the patient for minimum of 72 hours prior to the Lead-In infusion. The patch is water resistant and can be worn in the shower by the patient. The patch will be removed prior to the first infusion of study drug.

In addition to the above, the following procedures will be performed:

- Obtain signed main study ICF (must be obtained prior to performance of any study-specific tests or evaluations that are not considered standard of care).
- Confirm inclusion/exclusion criteria

- History of qualifying hemodynamics
- Conduct a medical history
- Body weight
- Record prior/concomitant medications including all prescription and non-prescription drugs, vitamins, and dietary or herbal supplements
- Record demographic information
- Perform complete physical examination, including height and body weight
- Urine pregnancy test (women of child-bearing potential only)
- Hematology and clinical chemistry blood samples
- Measure vital signs: BP, PR, respiratory rate, temperature
- Child-Pugh Class
- NYHA Functional Class
- Conduct 12-lead ECG
- Echocardiogram (within 3 months of Day 0)
    - Must be repeated prior to Baseline
- Perform 6MWT

8.2 Day 0 (Lead-in Infusion, Visit 1)

This visit may be performed on the same day as the Screening Visit if all procedures have been completed.

During the Lead-in Infusion (Day 0) the following procedures will be performed:

- Measure vital signs: BP, PR, respiratory rate, temperature
- Venous sheath placement for right heart catheterization. The sheath will remain following the baseline study, and the patient will be hospitalized where they will

receive the 24-hour levosimendan infusion (preferably through the venous sheath). The sheath will then be used for access for the right heart catheterization study following the 24-hour levosimendan infusion, and then removed (see Attachment 6).

- Right heart catheterization measurements: baseline (prior to levosimendan infusion) and post 24-hour infusion
    - Establish qualifying baseline hemodynamics at rest and exercise
    - Establish qualifying response to levosimendan during exercise
- Assess adverse events
- Assess concomitant medications and/or procedures
- Pharmacokinetic sampling (to be taken at the end of infusion: 24 ± 2 hours)
- Genotyping sample (to be taken at the end of insfusion: 24 ± 2 hours)

Subjects who do not respond to levosimendan based on hemodynamic measurements as defined in Section (7.5.3) will be withdrawn from screening. These subjects will be followed for safety, as outlined in section 8.7.

If subject is deemed a screen failure, the pharmacokinetic and genotyping samples do not need to be collected.

A PICC line will be placed in patients that meet eligibility criteria and who are randomized into the Double-Blind phase of the study.

8.3 Day 0 (Double-blind Randomization, Visit 1)

Once eligibility is confirmed via hemodynamic measurements per section 8.9.2, post lead-in infusion, subjects will be randomized 1:1 to either receive levosimendan or placebo. This will occur at the same visit as the lead-in dose (Day 0).

- Randomization via IWRS
- PICC line placement **(for randomized patients only)**

Follow-up in patients that are **not randomized**: Subjects that receive levosimendan during the Lead-In dose, but are not randomized into the trial, will followed for 2 weeks. Phone contact will be made with the subject by the investigational staff at 24 hours (+24 hours), 7 days (± 2 days), and 14 days (± 2 days) post Lead-In infusion.

8.4 Weeks 2-5 (Weekly Infusion Visits 2, 3, 4, and 5)

Visits at Weeks 2, 3, 4, and 5 should be performed within ± 48 hours of the scheduled visit. Visits for Weeks 2-5 should be calculated based on the date of the Lead-in infusion.

These visits will be performed at the subject's home with the aid of the home health care nurse.

The home health care nurse will remain with the patient for the first 2-3 hours of the infusion to ensure patient safety. The home health care nurse will visit the patient again at 24 hours to stop the infusion and assess the patient's status.

During visits where the home healthcare nurse is present, subjects may inform the nurse and/or investigator of any infusion related events or AEs. Questions regarding the infusion pump should be directed to the 24-hour Coram Pharmacy hotline.

During this visit, the following procedures will be performed:

- Record any changes in procedures, prescription and non-prescription drugs, vitamins, and dietary or herbal supplements
- Measure vital signs prior to starting the infusion, after the first 2 hours (±30 min), and after 24 hours (±30 min).
- Assess adverse events
- Study drug administration

At Week 5, all patients will be given a new cardiac monitoring sensor to wear on their chest to measure cardiac rhythm, as was done during Screening. This patch is to be applied prior to (< 1 hour) the 24-hour infusion will remain monitoring the patient for minimum of 72 hours and returned to the investigational site at the Week 6 visit.

8.5 Interim Office Visit (Between Weeks 3 and 4)

The Interim Office Visit should be performed 48 hours prior to the Week 4 Infusion visit. This visit will be performed at the investigator's office. Infusions will not occur at the office during these visits.

During this visit, the following procedures will be performed:

- 6MWT
- Quality of Life (QOL) assessment

- NYHA Functional Class determination
- Body weight
- Dispense cardiac monitoring patch
- All procedures listed in section 8.4 (with exception of infusion)

If no meaningful lowering of blood pressure is noted, or an increase in heart rate, the dose will be increased for all subjects to 0.10 µg/kg/min for 24 hrs. (see Attachment 5).

The home health care nurse will be notified by the site of confirmation of up-titration or any dose adjustments.

If for any reason the Interim Office Visit is not preformed, the dose level of levosimendan should remain at 0.075 µg/kg/min for 24 hrs.

8.6 Week 6 (Visit 6)

Visits at Week 6 should be performed 3-6 days following completion of the Week 5 infusion.

During this visit, the following procedures will be performed:

- Record any changes in procedures, prescription and non-prescription drugs, vitamins, and dietary or herbal supplements
- Measure vital signs: BP, PR, respiratory rate, temperature
- Hematology and clinical chemistry blood samples
- Conduct 12-lead ECG
- Echocardiogram within ±72 hours of the Week 6 visit
- Right heart catheterization at rest and with exercise (section 8.9.2 and Attachment 6)
- Quality of Life (QOL) assessment
- Child-Pugh Class
- NYHA Functional Class
- Assess adverse events
- Perform 6MWT

- Pharmacokinetic sampling (sample to be taken prior to enrollment in OL phase)

8.7 Early Termination

If a subject terminates the study prematurely, procedures listed in the Week 6 visit should be performed as soon as possible. The RHC, echocardiogram, and 6MWT do not need to be performed for subjects who terminate the study early.

Subjects will be followed for safety for 2 weeks after early termination. A phone contact will be made with the subject at 24 hours (+ 24 hours), 7 days (± 2 days), and 14 days (± 2 days) post infusion by investigational site personnel to assess any new or ongoing adverse events.

If a subject discontinues greater than 24 hours after their prior infusion, the 24-hour phone contact does not need to be performed and the next phone contact beginning at 7 days should be completed.

The vital status of all subjects will be collected at the end of the trial, regardless of reason for discontinuation.

8.8 Open Label Extension

Randomized subjects will have the option to enter into an open-label study following the completion of all study procedures at Week 6. If a subject decides not to continue in the open label protocol after Week 6, safety follow up phone call procedures listed in section 8.7 should be followed.

8.9 Study Evaluations and Procedures

Study procedures will occur according the Time and Events Schedule.

8.9.1 Demographic and Other Baseline Characteristics

Demographics including date of birth, ethnicity and sex will be collected at the Screening visit.

8.9.2 Efficacy Measures

8.9.2.1 Right Heart Catheterization

Subjects will have hemodynamic measurements assessed at the Day 0 (pre and post infusion) and Week 6 visits. For inclusion into the study, a subject must have a mean pulmonary arterial pressure (mPAP) of ≥ 35 mmHg and a pulmonary capillary wedge pressure (PCWP) of ≥ 20 mmHg.

Measurements will be recorded via RHC in the following sequence: as the subject is supine, legs elevated, and supine with bicycle exercise (25 watts). See Attachment 6 for procedure.

Subjects who qualify for the study will have a PICC line inserted for the Double-Blind phase of the study (i.e., prior to the Week 2 infusion).

8.9.2.2 6-Minute Walk Test (6MWT)

The 6MWT should be performed at approximately the same time of day at each study visit after the Baseline Visit and ideally, one of the first assessments to be performed. The ECHO and subject questionnaire should be performed after the 6MWT has been completed. Patients who discontinue study drug prior to Week 6 should continue to have all safety and efficacy assessments performed as scheduled through the Week 6 Visit, unless contraindicated.

The 6MWT will be performed at the time points specified in the Time and Events Schedule using the methods described in the American Thoracic Society (ATS) Statement: Guidelines for the Six-Minute Walk Test (50). Testing should be performed in a location where a rapid, appropriate response to an emergency is possible. The appropriate location of a crash cart should be determined by the physician supervising the facility. The test should be performed at approximately the same time of day when assessed and by the same evaluator whenever possible.

8.9.2.3 Echocardiogram Complete with Contrast

The 2-dimensional (2D) echocardiogram complete with contrast will be performed by trained personnel at the time points specified in the Time and Events Schedule.

These assessments will be standard transthoracic 2D echocardiograms (with contrast to optimize accuracy and precision of intracardiac measurements). Details of specific measurements and plans for analysis will be included in the core lab analysis plan.

These may include, but are not limited to:

1. Left ventricular: systolic and diastolic function; size, mass, and geometry.
2. Right ventricular size and function; pulmonary artery size.
3. Left atrial dimensions, volumes, and pressures.
4. Valvular (aortic, mitral, tricuspid and pulmonary) stenosis and regurgitation (severity).
5. Pulmonary artery systolic pressure (PASP), Inferior vena cava (IVC) calibre

8.9.3 Safety, Pharmacokinetic, and Pharmacogenomic Assessments

All safety evaluations will be performed at the time points listed in the Time and Events Schedule.

8.9.3.1 Medical and Medication History

To be completed at the Screening Visit to ensure subjects meet the inclusion criteria for the study. Any clinically significant history should be noted in the eCRF.

8.9.3.2 Physical Examination (Including Height and Weight)

Abnormalities identified at the Screening Visit will be documented in the subject's source documents and on the medical history eCRF. Changes after the Screening Visit will be captured as AEs on the AE eCRF page, as deemed by the Investigator.

8.9.3.3 Adverse Event Collection

Adverse events will be reported by the subject (or, when appropriate, by the subject's physician, a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Non-serious adverse events will be followed by the investigator from the signing of the Informed Consent until Week 6 or discontinuation of the study, whichever occurs first. Serious adverse events will be collected through Week 6. Specific details on adverse event reporting are provided in Section 9.

8.9.3.4 Vital Signs

Blood pressure should be determined by cuff (using the same method, the same arm, and in the same position throughout the study). Any clinically significant deviations from baseline vital signs which are deemed clinically significant in the opinion of the Investigator are recorded as an AE.

Vital signs and body weight should be recorded according to the Time and Events Schedule and include: body temperature, heart rate, respiratory rate, and blood pressure [systolic and diastolic blood pressure].

8.9.3.5 Clinical Laboratory Evaluations

All blood laboratory test collections must be performed **prior to** study drug dosing (where other exclusions do not apply). Blood specimens for hematology and serum chemistry will be collected, and results obtained by local laboratories, except for the pharmacokinetic and genotyping samples. These samples will be sent to external labs for analysis of Levosimendan, OR-1855 and OR-1896 metabolites.

All clinical laboratory assays will be performed according to the laboratory's normal procedures. Reference ranges are supplied by the laboratory and used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The Investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant (NCS) or clinically significant (CS).

Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition may be, at the discretion of the Investigator or Sponsor, repeated until confirmed, explained, or resolved as soon as possible.

Blood samples for hematology and serum chemistry will be taken at the time points detailed in the Time and Events Schedule. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. The following tests may be performed by the local laboratories and results entered into the eCRF, as shown in the Time and Events Schedule:

Hematology and Coagulation Panel

Hematocrit
Hemoglobin
White blood cell (WBC) count with differential
Platelet count
Prothrombin time
Partial thromboplastin time

Serum Chemistry Panel

Sodium
Potassium
Bicarbonate
Blood urea nitrogen (BUN)
Creatinine

8.9.3.6 Pregnancy Test

For female subjects with childbearing potential, a urine or serum pregnancy test will be performed at the Screening Visit. Results must be available before study drug administration. Additional serum or urine pregnancy testing may be performed as required by local regulations (if performed, pregnancy tests must be negative for subjects to continue in the study).

8.9.3.7 Electrocardiogram

Subjects should have a 12-lead ECG performed at Screening and Week 6. ECGs should be performed prior to administration of study drug (where applicable). Abnormal ECGs may be repeated at the Investigator's discretion.

8.9.3.8 Clinical Pharmacology Assessments

Pharmacokinetic sampling will occur at the Day 0 and Week 6 visits. These samples will be sent to a central laboratory for testing. The name and address of the clinical pharmacology laboratory used in this study will be maintained in the Investigator's files at each site.

Complete instructions for sample processing, handling and shipment will be provided in the Laboratory Manual.

8.9.3.9 Pharmacogenomic Assessments

Genetic sampling will occur at the Day 0 visit. The purpose of this sample is to determine acetylation status (rapid, slow) and will not be used for further research.

These samples will be sent to a central laboratory for testing. The name and address of the pharmacogenomic laboratory used in this study will be maintained in the Investigator's files at each site.

Subjects will provide an additional blood sample at Day 0. Donation of samples is optional, has no impact on participation in the main study. To ensure subject confidentiality samples will be stored and analyzed in a de-identified format.

Subjects have the right to withdraw consent from this additional component, with no impact on participation in the main study. Any results generated will not be made available, unless required to do so by law. Subjects can request results of any analysis on their samples, although it won't be possible to interpret these. No record of participation in this pharmacogenomics portion of the protocol, or any results derived from it, should be recorded in the subjects' medical records. A record of participation in the pharmacogenomics portion of the protocol will, however, be captured in the study-specific source documentation records or eCRF.

Complete instructions for sample processing, handling and shipment will be provided in the Laboratory Manual.

8.9.3.10 Quality of Life Assessments

A six-point Likert scale will be provided to subjects to complete at the Week 3 Office Visit and the Week 6 Visit.

8.10 Retention of Testing Samples

Samples will be retained for at least 5 years following the date of the New Drug Application (NDA) or supplemental NDA approval or if the Investigational New Drug (IND) is discontinued, at least 5 years following the date of completion of the study.

9. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

9.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1994).

All AEs are collected from the time the informed consent is signed until the subject discontinues or until Week 6 (whichever is first) and are to be recorded on the appropriate AE pages in the eCRF and in source documents. AEs will continue to be followed and collected during the Open-Label phase of the trial. Where possible, a diagnosis, rather than a list of symptoms, should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), an outcome is reached, stabilization (the Investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained regardless of whether the subject is still participating in the study. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

9.1.1 Severity Categorization

The severity of AEs must be recorded during the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate eCRF).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

9.1.2 Relationship Categorization

A Physician/Investigator must make the assessment of relationship to investigational product for each AE. The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as 'not related'. Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered 'related'. The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship	Definition
Related	Yes	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	No	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

9.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the eCRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

9.1.4 Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classed as AEs if they are within the normal day-to-day fluctuation or expected progression of the disease. However, significant worsening of the symptoms should be recorded as an AE.

Adverse events should not be recorded in the eCRF if they are represented by any of the following:

Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion); however, the condition that required the procedure is considered an adverse event if the situation developed or worsened after enrollment into the study.

Pre-existing diseases or baseline conditions present or detected at the start of the study that do not worsen.

Situations where an untoward medical occurrence has not taken place (e.g., hospitalization for elective surgery, social or convenience admissions).

9.1.5 Study-specific Events of Interest

Duration, course, and any medical intervention or dose adjustment will be captured in the eCRF. All study-specific events of interest should also be assessed for serious adverse event criteria (refer to section 9.2.3) and reported on the appropriate eCRF.

Hypotension

Since there is no single blood pressure measurement that will define hypotension for all study subjects, hypotension is to be recorded as an event of interest if the observed decrease in blood pressure was more than what the investigator anticipated.

In the conscious subject, whenever hypotension is recorded as an adverse event, it is to be classified as either a significant decrease in SBP **or** sufficiently low blood pressure defined as ≤ 80 mmHg.

Atrial Fibrillation

New-onset of persistent atrial fibrillation requiring intervention.

Other Clinically Significant Arrhythmias

Except for new-onset atrial fibrillation, clinically significant arrhythmias will be defined as any rhythm that requires medical intervention such as pacing, or the addition, removal, or dose adjustment of any drugs in an attempt to treat the abnormal rhythm.

Aborted Resuscitated Death

The incidence of survival following a cardiac arrest.

Stroke

Stroke will be defined as a new the rapid onset of a new neurological deficit of cerebrovascular cause that persists beyond 24 hours (non-fatal) or is interrupted by death within 24 hours (any) with evidence of new neurological lesion on imaging modalities.

9.1.6 Clinical Laboratory Evaluations

A change in the value of a clinical laboratory investigation can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory values which were not present at baseline, further clinical or laboratory investigations should be performed until the values return to within the reference range or until a plausible explanation (e.g., concomitant disease) is found for the abnormal clinical laboratory values.

The Investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory parameter is clinically significant and therefore represents an AE.

9.1.7 Pregnancy

All pregnancies are to be reported from the time first infusion of study drug is received until the subject discontinues the study.

Any report of pregnancy for any female study participant must be reported within 24 hours to the Medpace Pharmacovigilance Department using the Medpace Pregnancy Report Form.

The female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the Investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the provided SAE form. Note: An elective abortion is not considered an SAE.

In addition to the above, if the Investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the provided SAE form as well as the Pregnancy Report

Form. The test date of the first positive serum/urine HCG test or ultrasound result will determine the pregnancy onset date.

In animal studies, levosimendan was not teratogenic, but it caused a generalized reduction in the degree of ossification in rat and rabbit fetuses with anomalous development of the supraoccipital bone in the rabbit. When administered before and during early pregnancy, levosimendan reduced fertility (decreased the number of corpora lutea and implantations) and exhibited developmental toxicity (decreased pups per litter and increased the number of early resorptions and post-implantation losses) in the female rat. The effects were seen at clinical exposure levels.

9.1.8 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the Sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 9.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than one category.

- **Abuse** – Persistent or sporadic intentional intake of the investigational product when used for a non-medical purpose (e.g., to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.
- **Misuse** – Intentional use of the investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol).
- **Overdose** – Intentional or unintentional intake of a dose of an investigational product exceeding a prespecified total daily dose.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the Sponsor only as defined below.

Cases of subjects missing doses of product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of an expired product should be considered as a reportable medication error.

To prevent possible medication errors or miscalculations, refer to Attachment 1 of this protocol before administration of study drug

9.2 Serious Adverse Event Procedures

9.2.1 Reference Safety Information

The reference for safety information for this study is the Investigator's Brochure/Summary of Product Characteristics/SmPC which the Sponsor has provided to all Investigators.

9.2.2 Reporting Procedures

Initial Reports

All SAEs must be reported to Medpace Clinical Safety **within 24 hours** of the knowledge of the occurrence.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE hotline (phone number listed below), and fax/email the completed paper SAE form to Medpace (contact information listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Follow-Up Reports

The investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment) or the subject dies.

Within 24 hours of receipt of follow-up information, the investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., subject discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

Safety Contact Information:
Medpace Clinical Safety

Medpace SAE hotline – USA:
Telephone: +1-800-730-5779, dial "3" **or** +1-513-579-9911, dial "3"
Facsimile: +1-866-336-5320 **or** +1-1-513-570-5196
E-mail: medpace-safetynotification@medpace.com

Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless they result in an SAE.

9.2.3 Serious Adverse Event Definition

A Serious Adverse Event (SAE) is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening

  NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event; Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in subject hospitalization; or the development of drug dependency or drug abuse.

Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, admission for a previously scheduled ventral hernia repair would not be classified as an SAE.

However, complication(s) resulting from hospitalization for an elective or previously scheduled surgery that meets serious criteria must be reported as SAE(s).

9.2.4 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject prior to study entry or leading up to the onset date of the SAE or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

9.2.5 Fatal Outcome

Any SAE that results in the subject's death (i.e., the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product).

9.2.6 Regulatory Agency, Institutional Review Board, and Site Reporting

The Sponsor is responsible for notifying the relevant regulatory authorities/US central Institutional Review Boards (IRBs) of related, unexpected SAEs.

In addition, the Sponsor (or designee) is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the program.

The Investigator is responsible for notifying the local IRB, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

9.2.7 Serious Adverse Event Collection Timeframe

All SAEs (regardless of relationship to study) are collected from the time the subject signs informed consent until the subject discontinues the study or Week 6 (whichever comes first) and must be reported to the Medpace Pharmacovigilance Department within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the Investigator at any interval after the study has completed must be reported to the Med Pace Pharmacovigilance Department within 24 hours of the first awareness of the event.

SAEs will be collected for subjects who continue to receive study drug in the Open-Label phase of the study, post Week 6, until they discontinue use of Levosimendan for purposes related to this protocol.

10. DATA MANAGEMENT AND STATISTICAL METHODS

10.1 Data Collection

The Investigators' authorized site personnel must enter the information required by the protocol on the eCRF. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel.

When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the Investigator's Meeting (if applicable). It is expected that site personnel will complete the eCRF entry within five business days of the subject's visit.

10.2 Clinical Data Management

Data collected. eCRF will follow certain pre-set standards. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are to be documented in an auditable manner.

Hemodynamic data recorded by clinical staff during the required right heart catheterization measurements will undergo a central adjudication (blinded by patient, treatment, time, and site) by reviewing the electronic tracing captured during right heart catheterization and provided by the clinical site. The adjudicated data will be used in the final data analyses.

10.3 Statistical Analysis Process

Details regarding the statistical methods and definitions will be provided in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to unblinding to preserve the integrity of the statistical analysis and study conclusions. All statistical analyses will be performed after the database is locked and unblinded. Statistical analyses will be performed using Version 9.33 or higher of SAS® (SAS Institute, Cary, NC 27513).

10.4 Selection of Subjects to be Included in the Analyses

Screened Set – The set of subjects who have signed informed consent.

Enrolled Set – Subjects who have signed informed consent and met open-label lead-in inclusion-enrollment criteria.

Randomized Set – Enrolled subjects who met the inclusion-randomization criterion as responders to levosimendan for whom a randomization number has been assigned.

Safety Analysis Set – Enrolled/Randomized subjects who received any study drug

Full Analysis Set – Randomized subjects who received any study drug and completing the study with Week 6 office visit.

Per-Protocol Set – Subjects in the Full Analysis Set who have completed the final scheduled primary assessment for the study and do not have pre-defined major protocol deviation.

Pharmacokinetic Set – Subjects in the Full Analysis Set for whom the primary pharmacokinetic data is considered sufficient and interpretable.

10.5 Subject Disposition

Subjects in each analysis set, as well as subjects who complete the study, and subjects who prematurely discontinue from the study will be summarized by treatment group using descriptive statistics. In addition, for subjects who prematurely discontinue from the study, the reasons for discontinuation will be summarized by treatment group. Note: Subjects who discontinue the study prior to the Week 6 office visit will be replaced to ensure 18 randomized subjects in both arms (levosimendan, placebo) have completed the study for the primary analysis.

10.6 Demographic and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented by treatment group and overall for the Safety Analysis Set and Full Analysis Set.

Demographics and baseline characteristics will be examined to assess the comparability of the treatment groups at baseline. Continuous variables such as subject age, weight, height, and body mass index (BMI) will be summarized using number of observations, mean, standard deviation, median, minimum, and maximum values. Categorical variables such as subject sex and race will be summarized using number of observations and percentages for each category.

Medical history will be summarized by treatment group using the number of observations and percentages of subjects reporting each category.

10.7 Investigational Product Exposure

Summary statistics for the duration of exposure to investigational product will be presented by treatment group. The number of subjects receiving each dose will be summarized by treatment group and by visit in the study. Compliance rates will be summarized by treatment group at each visit.

10.8 Prior and Concomitant Medication

Prior and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary. Prior and concomitant medications will be listed and summarized by preferred drug name and treatment group.

10.9 Efficacy Analyses

All efficacy analyses will be based on the Full Analysis Set and all statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance. Also, all confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

10.9.1 Primary Efficacy Variable

The primary efficacy variable is defined as the change from baseline PCWP with bicycle exercise (25 watts) at 6 weeks. The baseline PCWP with bicycle exercise (25 watts) is defined as the value obtained prior to lead-in study drug infusion on Day 0.

The primary efficacy analysis will be conducted over the Full Analysis Set. The PCWP will be analyzed using an analysis of covariance (ANCOVA) model with change from baseline to Week 6 in PCWP as dependent variable, treatment group and analysis site as factors.

For patients who withdraw before Week 6 endpoint, multiple imputation methods with missing at random and missing not at random will be used. A sensitivity analysis will include an adjustment for baseline. An additional analysis will be performed on the Full Analysis Set that met recruitment criteria and received all weekly infusions, the Per-Protocol Set.

10.9.2 Secondary Efficacy Variables

The following secondary variables will be assessed in this study.

- Change in Cardiac Index at rest and with exercise at Week 6
- Change in PVR effect at rest and with exercise at Week 6
- Change in PCWP when supine and legs elevated at Week 6
- Patient global assessment (based on a six-point Likert scale) at Week 6
- Exercise duration 6-min walk test at Week 6
- Physician's Assessment of Functional Class
- Clinical Events: Death and hospitalizations

Analyses will be performed on the Full Analysis Set. Hemodynamic responses during the initial lead-in infusion will be summarized using descriptive statistics for all subjects receiving levosimendan and in PH-HFpEF strata. The hemodynamic variables will be analyzed using the same ANCOVA model as the primary endpoint. A sensitivity analysis will include an adjustment for baseline. All secondary analyses will be performed in the Full

Analysis Set. Exercise tolerance differences will be tested using an ANOVA with effects for treatment and investigative site. Treatment differences in the subjects' response identified by Likert Scale will be analyzed by a Mann–Whitney–Wilcoxon test.

10.9.3 Exploratory Efficacy Variables

- Change in echo measurements of RV size and TAPSE

A description of the analyses will be included in the SAP.

10.10 Safety Analyses

Adverse events will be coded using MedDRA. The number of events, incidence, and percentage of treatment-emergent adverse events (TEAE) will be calculated overall, by system organ class (SOC), and by preferred term. Treatment-emergent adverse events will be further summarized by severity and relationship to the investigational product. Adverse events related to the investigational product, AEs leading to withdrawal, SAEs, and deaths will be summarized/listed.

Clinical laboratory tests, vital signs, and ECG findings will be summarized by treatment group and visit. Potentially clinically important findings will also be summarized or listed.

10.11 Pharmacokinetic Collection and Analyses

Pharmacokinetic samples will be collected post-infusion (24±2 hrs.) post Lead-in infusion and at the Week 6 visit. Analysis will occur via a central laboratory.

10.12 Sample Size Calculation and Power Considerations

The sample size was estimated for the primary comparison of levosimendan and placebo using SAS (v9.4) for windows procedure PROC POWER.

A total of 36 randomized subjects (at 1:1 levosimendan vs. placebo) will provide 80% power to detect the difference at two-sided 0.05 level, assuming an SD of 5 mmHg in PCWP and a treatment difference of ≥4.9 mmHg.

Randomized subjects that have not received study drug weekly through Week 5 and returned for evaluation on Week 6 will be replaced to ensure 18 subjects have completed in each study group.

11. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, and local ethical and legal requirements.

11.1 Sponsor's Responsibilities

11.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations and ICH Good Clinical Practice (GCP) Guideline E6 (1996).

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the Sponsor to inspect study data, subjects' medical records, and eCRFs in accordance with current GCP and the respective local and inter/national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The Sponsor ensures that Local Regulatory Authority requirements are met before the start of the study. The Sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any Regulatory Authority approvals required prior to release of investigational product for shipment to the site.

11.1.2 Public Posting of Study Information

The Sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating Investigators' names and contact information.

11.1.3 Study Suspension, Termination, and Completion

The Sponsor may suspend or terminate the study or part of the study at any time for any reason. If the study is suspended or terminated, the Sponsor will ensure that applicable regulatory agencies and IRBs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

11.2 Investigator's Responsibilities

11.2.1 Good Clinical Practice Compliance

The Investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (R2) 2016, and applicable regulatory requirements and guidelines.

It is the Investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to committing to participate in this study. The Investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The Investigator will maintain a list of appropriately qualified persons to whom the Investigator has delegated significant study-related tasks. *Curriculum vitae* for Investigators and sub-investigators are provided to the study Sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the Investigator should, with the subject's consent, inform them of the subject's participation in the study.

A Coordinating Principal Investigator is appointed to review the final Clinical Study Report for multi-site studies. Agreement with the final Clinical Study Report is documented by the signed and dated signature of the Coordinating Principal Investigator, in compliance with ICH Guidance E3 (1995).

11.2.2 Protocol Adherence and Investigator Agreement

The Investigator and any co-investigators must adhere to the protocol as detailed in this document. The Investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an Investigator Agreement to confirm acceptance and willingness to comply with the study protocol.

If the Investigator suspends or terminates the study at their site, the Investigator will promptly inform the Sponsor and the IRB and provide them with a detailed written explanation. The Investigator will also return all investigational product, containers, and other study materials to the Sponsor. Upon study completion, the Investigator will provide the Sponsor, IRB, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs, to ensure accurate and timely information is provided at all phases during the study, may be done by the Sponsor, applicable CRO, Investigator, or for multi-site studies, the Coordinating Principle Investigator according to national provisions and will be documented in the Investigator Agreement.

11.2.3 Documentation and Retention of Records

11.2.3.1 Case Report Forms

The electronic Case Report Form (eCRF) is supplied by Medpace and should be handled in accordance with instructions from the Sponsor.

The Investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case Report Forms must be completed by the Investigator or designee as stated in the site delegation log. All data will have separate source documentation; no data should be recorded directly onto the eCRF.

All data sent to the Sponsor must be endorsed by the Investigator.

The CRA/Study Monitor will verify the contents against the source data per the Monitoring Plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

11.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but is not limited to: subject's medical file, subject quality of life assessments, original clinical laboratory reports, and histology and pathology reports.

All key data must be recorded in the subject's medical records.

The Investigator must permit authorized representatives of the Sponsor, the respective national, local, or foreign regulatory authorities, the IRB, and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/Study Monitor (and auditors, IRB or regulatory inspectors) may check the eCRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the Sponsor or its representatives, national or local regulatory authorities, or the IRB having access to source data (e.g., subject's medical file, appointment books, original laboratory reports, X-rays, etc.).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (e.g., the US Food and Drug Administration [FDA], European Medicines Agency [EMA], UK Medicines and Healthcare Products Regulatory Agency [MHRA]) or an auditor).

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the Sponsor.

11.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the MHRA, other regulatory authorities, the Sponsor or its representatives, and the IRB for each site.

11.2.3.4 Financial Disclosure

The Investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the value of the compensation for conducting the study could be influenced by the outcome of the study. The following information is collected: any significant payments from the Sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any

proprietary interest in investigational product; any significant equity interest in the Sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

In consideration of participation in the study, the Sponsor pays the Investigator or nominated payee the sums set out in the payment schedule attached to the Investigator agreement.

11.3 Ethical Considerations

11.3.1 Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from all study subjects prior to any study related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally-authorized representative as applicable is requested to sign the Informed Consent Form (ICF) or a certified translation, if applicable after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (i.e., a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally-authorized representative as applicable. If applicable, it is provided in a certified translation of the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The Investigator provides the Sponsor with a copy of the consent form which was reviewed by the IRB and which received their favorable opinion/approval. A copy of the IRB's written favorable opinion/approval of these documents must be provided to the Sponsor, prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (i.e., Sponsor or Coordinating Principal Investigator) is responsible for this action. Additionally, if the IRB requires modification of the template ICF provided by the Sponsor, the documentation supporting this requirement must be provided to the Sponsor.

11.3.2 Institutional Review Board

It is the responsibility of the Investigator to submit this protocol, the informed consent document (approved by the Sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB for review, and all must be approved prior to site initiation.

Responsibility for coordinating with IRBs is defined in the Investigator Agreement.

Prior to implementing changes in the study, the Sponsor and the IRB must approve any revisions of any revised informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the Sponsor has received written IRB approval of and copies of revised documents.

The Investigator is responsible for keeping the IRB appraised of the progress of the study and of any changes made to the protocol, but in any case, at least once a year. The Investigator must also keep the local IRB informed of any serious and significant AEs.

11.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). A site that is not a Covered Entity as defined by HIPAA must provide documentation of this fact to the Sponsor.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the Sponsor and/or its representatives review their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the Sponsor; third parties with whom the Sponsor may develop, register, or market levosimendan; national or local regulatory authorities; and the IRB(s) which gave approval for the study to proceed. The Sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number. However, their initials and date of birth may also be collected and used to assist the Sponsor to verify the accuracy of the data, for example, to confirm that laboratory results have been assigned to the correct subject.

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies to the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results or to answer questions asked by regulatory or health authorities.

11.5 Publication Policy

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the Sponsor, in advance of submission. The review is aimed at protecting the Sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

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13. APPENDICES

13.1 APPENDIX 1: Summary of Changes to Previous Protocol Amendments

Revisions included in Amendment 3 to the protocol, dated 15 May 2019 (Version 4.0)

Page (redline version)	Section	Revisions Made (rationale for protocol revisions) Legend: unaltered text**, ~~deleted text~~**, new text
		Please Note: Administrative changes are shaded
Global Change		Revised reference to Protocol amendment and date: Version 4.0, 15 May 2019
12	**Enrollment Criteria:**	(revised qualifying hemodynamic criteria to clarify the values may be observed at rest or with legs up at baseline right heart catheter (Lead-In) 3. WHO Group 2 Pulmonary Hypertension subjects with heart failure and preserved ejection fraction as defined by: a. Mean pulmonary arterial pressure (mPAP) ≥35 mmHg at rest or with legs up (at baseline right heart catheter, Lead-In) b. Pulmonary capillary wedge pressure (PCWP) ≥20 mmHg at rest or with legs up (at baseline right heart catheter, Lead-In)
12	**Enrollment Criteria:**	(the qualifying range of six-minute walk test at baseline was expanded as the initial range was determined to be too restrictive and limited enrollment of patients that would otherwise qualify) 5. Ability to walk at least ~~100~~ 50 meters, but not more than ~~400~~ 550 meters in a six-minute walk test.
12	**Enrollment Criteria:**	(deleted the last phrase to elimate any confusion in the criterion. The only delivery route for oxygen is nasal cannula.) 6. Long term oxygen treatment (if applicable) must be stable for 30 days prior to enrollment~~, including delivery route and dose~~.

12	**Enrollment Criteria:**	(added to allow modification of antihypertensives medications prior to enrollment) 7. Subjects on a chronic medication or therapy for any underlying cardiac condition must be on a stable dose for ≥30 days prior to randomization, with the exception of diuretics and antihypertensive medication for blood pressure control which may be discontinued if deemed appropriate.
12	**Enrollment Criteria:**	(added Note to clarify interpretation of the term "stable" as used in Inclusion Crierion 6-8.) Note: With regard to Inclusion Criteria 6-8, "stable" refers to changes in oxygenation therapy or medications no greater than a 100% increase or a 50% decrease, as needed to optimize the patient.
13	**Exclusion Criteria:**	(clarified that a negative stress test applies to previous CABG cardiac surgery patients) 1. Previous PCI or cardiac surgery (CABG/~~valve~~) unless documented to have a negative stress test within the last 12 months.
13	**Exclusion Criteria:**	(reduced the period required since surgical correction of congenital disease with pre and post tricuspid shunts) 5. Congenital heart disease other than surgically corrected pre and post tricuspid shunts for at least ~~10~~ 5 years
13	**Exclusion Criteria:**	(removed redundancy in text) 6. Symptomatic coronary artery disease ~~and/or CAD~~ based on a positive stress test.
13	**Exclusion Criteria:**	(expanded to incorporate published standards for obstructive and restrictive lung disease in obese patients that are otherwise eligible for the study) 8. Patients diagnosed with pulmonary hypertension ~~secondary to~~ associated with clinically significant lung disease at the time of initial diagnosis, or patients with a congenital defect of the lung, ~~patients with severe obstructive lung disease (FEV1 <60% of predicted), or patients with severe restrictive lung disease (FVC of <70% of predicted)~~. a. Clinically significant obstructive lung disease is defined as FEV1/FVC <60% of predicted, unless a high resolution chest CT scan shows no more than mild areas of emphysematous changes. b. Clinically significant restrictive lung disease is defined as disease a FVC of <60% of predicted, unless a high resolution chest CT scan shows no more than mild areas of interstitial lung disease or pulmonary fibrosis.

13	**Exclusion Criteria:**	(expanded weight range to include those patients between 135 and 150 kg that can be effectively managed on the cath lab table) 13. Weight >~~135~~150 kg
17	**Footnotes for Time and Events Schedule**	(corrected typographical error in Weeks 2, 3, 4, 5, and 6 vist window) 11. Visits at Weeks 2, 3, 4, 5, and 6 should occur within +~~24~~48 hours of the scheduled visit (section 8.4).
27	**4.1 Inclusion Criteria** **Enrollment Criteria:**	(revised qualifying hemodynamic criteria to clarify the values must be observed at rest or with legs up at basleine (Lead-In) 3. WHO Group 2 Pulmonary Hypertension subjects with heart failure and preserved ejection fraction as defined by: a. Mean pulmonary arterial pressure (mPAP) ≥35 mmHg at rest or with legs up (at baseline right heart catheter, Lead-In) b. Pulmonary capillary wedge pressure (PCWP) ≥20 mmHg at rest or with legs up (at baseline right heart catheter, Lead-In)
27	**4.1 Inclusion Criteria** **Enrollment Criteria:**	(the qualifying range of six-minute walk test at baseline was expanded as the initial range was determined to be too restrictive and limited enrollment of patients that would otherwise qualify) 5. Ability to walk at least ~~100~~ 50 meters, but not more than ~~400~~ 550 meters in a six-minute walk test.
27	**4.1 Inclusion Criteria** **Enrollment Criteria:**	(deleted the last phrase to elimate any confusion in the criterion; the only delivery route for oxygen is nasal cannula) 6. Long term oxygen treatment (if applicable) must be stable for 30 days prior to enrollment~~, including delivery route and dose~~.
28	**4.1 Inclusion Criteria** **Enrollment Criteria:**	(added to allow modification of antihypertensives medications prior to enrollment) 7. Subjects on a chronic medication or therapy for any underlying cardiac condition must be on a stable dose for ≥30 days prior to randomization, with the exception of diuretics and antihypertensive medication for blood pressure control which may be discontinued if deemed appropriate.
28	**4.1 Inclusion Criteria** **Enrollment Criteria:**	(added Note to clarify interpretation of the term ”stable” as used in Inclusion Crierion 6-8.) Note: With regard to Inclusion Criteria 6-8, “stable” refers to changes in oxygenation therapy or medications no greater than a 100% increase or a 50% decrease, as needed to optimize the patient.
28	**4.2 Exclusion Criteria**	(clarified that a negative stress test applies to previous CABG cardiac surgery patients)

		1. Previous PCI or cardiac surgery (CABG/~~valve~~) unless documented to have a negative stress test within the last 12 months.
28	**4.2 Exclusion Criteria**	(reduced the period required since surgical correction of congenital disease with pre and post tricuspid shunts) 5. Congenital heart disease other than surgically corrected pre and post tricuspid shunts for at least ~~10~~ 5 years
28	**4.2 Exclusion Criteria**	(removed redundancy in text) 6. Symptomatic coronary artery disease ~~and/or CAD~~ based on a positive stress test.
29	**4.2 Exclusion Criteria**	(expanded to incorporate published standards for obstructive and restrictive lung disease in obese patients that are otherwise eligible for the study) 8. Patients diagnosed with pulmonary hypertension ~~secondary to~~ associated with clinically significant lung disease at the time of initial diagnosis, or patients with a congenital defect of the lung, ~~patients with severe obstructive lung disease (FEV1 <60% of predicted), or patients with severe restrictive lung disease (FVC of <70% of predicted)~~. a. Clinically significant obstructive lung disease is defined as FEV1/FVC <60% of predicted, unless a high resolution chest CT scan shows no more than mild areas of emphysematous changes. b. Clinically significant restrictive lung disease is defined as disease a FVC of <60% of predicted, unless a high resolution chest CT scan shows no more than mild areas of interstitial lung disease or pulmonary fibrosis.
29	**4.2 Exclusion Criteria**	(expanded weight range to include those patients between 135 and 150 kg that can be effectively handeled on the cath lab table) 13. Weight >~~135~~150 kg
36	**7.5.5 Blinding the Treatment Assignment**	(deleted text in conflict with previous sentence) ~~It is not required to use the protective sheath during the Lead-In infusion.~~
44	**8.4 Weeks 2-5 (Weekly Infusion Visits 2, 3, 4, and 5)**	(added window to vital sign measurements at 2 hours and 24 hours at weekly infusion visits) • Measure vital signs prior to starting the infusion, after the first 2 hours (±30 min), and after 24 hours (±30 min).

Revisions included in Amendment 2 to the protocol, dated 25 January 2019 (Version 3.0)

Page (redline version)	Section	Revisions Made (rationale for protocol revisions) Legend: unaltered text, ~~deleted text~~, new text
		Please Note: Administrative changes are shaded
Global Change		Revised reference to Protocol amendment and date: Version 3.0, 25 January 2019
12	**Enrollment Criteria:**	(deleted reference to NHYA Subclass II"b" as the distinction is not universally accepted, raising questions of interpretation) 3. WHO Group 2 Pulmonary Hypertension subjects with heart failure and preserved ejection fraction as defined by: c. NYHA Class II~~b~~ or III
13	**Exclusion Criteria:**	(added allowance for patients with history of previous PCI or cardiac surgery if there is documentation of a negative stress test in last 12 months.) 1. Previous PCI or cardiac surgery (CABG/valve) unless documented to have negative stress test within the last 12 months.
13	**Exclusion Criteria:**	(expanded to further clarify clinically significant lung disease) 8. ~~History of symptomatic COPD, restrictive lung disease, congenital defect of the lung, or other clinically significant lung disease~~ Patients diagnosed with pulmonary hypertension secondary to lung disease at the time of initial diagnosis, patients with a congenital defect of the lung, patients with severe obstructive lung disease (FEV1 <60% of predicted), or patients with severe restrictive lung disease (FVC of <70% of predicted).
13	**Exclusion Criteria:**	(clarified to note "symptomatic" elevation in SBP to be consistent with Appendix 5: Cardiac Event Recommendations and Management in the protocol, page 81)

		14. Symptomatic low ~~S~~systolic blood pressure (SBP) that cannot be managed to ensure SBP > 100 mmHg at initiation of study drug
13	**Exclusion Criteria:**	(clarified to note "symptomatic" elevation in HR to be consistent with Appendix 5: Cardiac Event Recommendations and Management in the protocol, page 81) 15. Heart rate ≥100 bpm with study drug, symptomatic and persistent for at least 10 minutes at Lead-in.
13	**Exclusion Criteria:**	(revised the length of time a patients must be off vasodilator therapy prior to randomization, as these drugs have short half-lives) 23. Concomitant administration of pulmonary vasodilator therapy, or taken within ~~30~~ 14 days of randomization.
16	**TIME AND EVENTS SCHEDULE** **Lead-In Infusion, Day 0 (Visit 1)**	(added to ensure lead-in dose based on a current body weight) Added "X" in "Lead In" column for "Body Weight"
16	**TIME AND EVENTS SCHEDULE** **Lead-In Infusion, Week 6**	(revised time window for Week 6 visit window as per the Administrative Letter 2.0, dated 5 November 2018; The timing of the Week 6 visit was revised to allow flexibility for cath lab scheduling. Rather than have the visit at the END of Week 6, the revised visit window recommends 3-6 days following completion of the Week 5 infusion to ensure that final hemodynamic measurements in the cath lab will be made during a period that coincides with the usual range in plasma levels of levosimendan's active metabolite, OR-1896.) Week 6 ~~(+ 48 hrs~~. 3 -6 days following completion of the Week 5 infusion.)
27	**Enrollment Criteria:**	(deleted reference to NHYA Subclass II"b" as the distinction is not universally accepted, raising questions of interpretation)

		3. WHO Group 2 Pulmonary Hypertension subjects with heart failure and preserved ejection fraction as defined by: c. NYHA Class II~~b~~ or III
27	**4.2 Exclusion Criteria**	(added allowance for patients with history of previous PCI or cardiac surgery if there is documentation of a negative stress test in last 12 months.) 1. Previous PCI or cardiac surgery (CABG/valve) unless documented to have a negative stress test within the last 12 months .
28	**4.2 Exclusion Criteria**	(expanded to further clarify clinically significant lung disease) 8. ~~History of symptomatic COPD, restrictive lung disease, congenital defect of the lung, or other clinically significant lung disease~~ Patients diagnosed with pulmonary hypertension secondary to lung disease at the time of initial diagnosis, patients with a congenital defect of the lung, patients with severe obstructive lung disease (FEV1 <60% of predicted), or patients with severe restrictive lung disease (FVC of <70% of predicted).
28	**4.2 Exclusion Criteria**	(clarified to note "symptomatic" elevation in SBP to be consistent with Appendix 5: Cardiac Event Recommendations and Management in the protocol, page 81) 14. Symptomatic low ~~S~~systolic blood pressure (SBP) that cannot be managed to ensure SBP > 100 mmHg at initiation of study drug
28	**4.2 Exclusion Criteria**	(clarified to note "symptomatic" elevation in HR to be consistent with Appendix 5: Cardiac Event Recommendations and Management in the protocol, page 81) 15. Heart rate ≥100 bpm with study drug, symptomatic and persistent for at least 10 minutes at Lead-in.
29	**4.2 Exclusion Criteria**	(revised the length of time a patients must be off vasodilator therapy prior to randomization, as these drugs have short half-lives) 23. Concomitant administration of pulmonary vasodilator therapy, or taken within ~~30~~ 14 days of randomization.
36	**7.5.5 Blinding the Treatment Assignment**	(Clarification to ensure the patient is consistently blinded to the appearance of administered study drug.)

		Protective sheaths for the infusion line and bag will be used to protect the study drug from UV light and are required to be used <u>at Lead-In</u> and during the Week 2 through 5 infusion visits. It is not required to use the protective sheath during the Lead-In infusion.
40	**8.1 Screening Visit (< 28 Days prior to Day 0)**	(added to ensure lead-in dose based on a current body weight) • <u>Body weight</u>
44	**8.6 Week 6 (Visit 6)**	(revised time window for Week 6 visit window as per the Administrative Letter 2.0, dated 5 November 2018; The timing of the Week 6 visit was revised to allow flexibility for cath lab scheduling. Rather than have the visit at the END of Week 6, the revised visit window recommends 3-6 days following completion of the Week 5 infusion to ensure that final hemodynamic measurements in the cath lab will be made during a period that coincides with the usual range in plasma levels of levosimendan's active metabolite, OR-1896.) Visits at Week 6 should be performed ~~within +48 hours of the scheduled visit~~<u>3-6 days following completion of the Week 5 infusion.</u>
58	**10.2 Clinical Data Management**	(added clarification that final analysis will be performed on hemodynamic data that have been adjudicated by a central reader) <u>Hemodynamic data recorded by clinical staff during the required right heart catheterization measurements will undergo a central adjudication (blinded by patient, treatment, time, and site) by reviewing the electronic tracing captured during right heart catheterization and provided by the clinical site. The adjudicated data will be used in the final data analyses.</u>

Revisions Amendment 1 to the protocol dated 10 July 2018 (Version 2.0)

Page (redline version)	Section	Revisions Made (rationale for protocol revisions) Legend: unaltered text, ~~deleted text,~~ new text
		Please Note: **administrative changes are shaded**
Global Change		Revised reference to Protocol amendment and date: version 2.0, 10 July 2018
16	**Time and Events Schedule**	(added body weight measurement at Interim Office Visit to allow modification of weight based dosing during trial) Body Weight added during Interim Office Visit.
17	**Footnotes for Time and Events Schedule**	(added to identify requirements for safety follow-up on subjects that receive an open-label lead-in dose who are NOT randomized, and the general requirements for safety follow-up of patients who terminate the study early.) 15. Subjects who receive levosimendan during the Lead-In dose but are not randomized into the trial, will be followed for safety for 2 weeks post end of 24-hour infusion. A phone contact will be made to the subject at 24 hours, 7 days, and 14 days post infusion by investigational site personnel to assess adverse events. Please see section 8.7 for further details regarding subjects who terminate the study early.
39	**8. STUDY PROCEDURES**	(added to clarify designation of study "Week" relative to initial dose in Open Label Lead-In) Visits for Week 2 through Week 6 should be calculated based on the date of the Lead-in infusion (not the date of randomization).
41	**8.2 Day 0 (Lead-in Infusion, Visit 1)**	(added reference to Attachment 6 that includes an added summary of right heart catheter measurement procedures in the cath label) • Venous sheath placement for right heart catheterization. The sheath will remain following the baseline study, and the patient will be hospitalized where they will receive the 24-hour levosimendan infusion (preferably through the venous sheath). The sheath will then be used for access for the right heart catheterization study following the 24-hour levosimendan infusion, and then removed (see Attachment 6).

42		(added to clarify baseline right heart catherization should be performed prior to levosimendan infusion) • Right heart catheterization measurements: baseline (prior to levosimendan infusion) and post 24-hour infusion
		(added to specify follow-up in patients who receive the lead-in levosimendan dose, but are NOT randomized) Subjects who do not respond to levosimendan based on hemodynamic measurements as defined in Section (7.5.3) will be withdrawn from screening. These subjects will be followed for safety, as outlined in section 8.7.
42	**8.3 Day 0 (Double-blind Randomization, Visit 1)**	(added to specify follow-up in patients who receive the Lead-in levosimendan dose, but are NOT randomized) Follow-Up in patients that are not randomized: Subjects that receive levosimendan during the Lead-In dose, but are not randomized into the trial, will followed for 2 weeks. Phone contact will be made with the subject by the investigational staff at 24 hours (+ 24 hours), 7 (+2) days, and 14 (+2) days post Lead-In infusion.
	8.4 Weeks 2-5 (Weekly Infusion Visits 2, 3, 4, and 5)	(added to clarify designation of study "Week" relative to initial dose in Open Label Lead-In) Visits for Weeks 2-5 should be calculated based on the date of the Lead-in infusion.
43	**8.5 Interim Office Visit (Between Weeks 3 and 4)**	(added body weight measurement to allow for adjustment of weight-based dosing during the study, and the requirement to provide subjects with the cardiac monitoring patch for in-home application during Week 5) • Body weight • Dispense cardiac monitoring patch
	8.6 Week 6 (Visit 6)	(added reference to Attachment 6 that includes an added summary of right heart catheter measurement procedures in the cath label) • Right heart catheterization at rest and with exercise (see section 8.9.2 and Attachment 6)
44	**8.7 Early Termination**	(added to specify follow-up for safety in those patients that terminate participation in the study prior to Week 6.) If a subject terminates the study prematurely, ~~all~~ procedures listed in the Week 6 visit should be performed as soon as possible. The RHC, echocardiogram, and 6MWT do not need to be performed for subjects who terminate the study early. Subjects will be followed for safety for 2 weeks. A phone contact will be made with the subject at 24 hours, (+24 hours) 7 days (±2 days), and

		14 days (±2 days) post infusion by investigational site personnel to assess adverse events. If a subject discontinues greater than 24 hours after their prior infusion, the 24-hour phone contact does not need to be performed and the next phone contact beginning at 7 days should be completed.
	8.8 Open Label Extension	(added to specify follow-up for safety in those patients that terminate participation in the study prior to Week 6.) If a subject decides not to continue in the open label protocol after Week 6, safety follow up phone call procedures listed in section 8.7 should be followed.
45	**8.9.2 Efficacy Measures** **Right Heart Catheterization**	(added to specify the sequence of positions/exercise sequence for measurements recorded via right heart catheterization at Day 0 (pre-and post- infusion) and Week 6) Measurements will be recorded via RHC in the following sequence: as the subject is supine, legs elevated, and supine with bicycle exercise (25 watts). See Attachment 6 for procedure.
47	**8.9.3.5 Clinical Laboratory Evaluations**	(added to specify that PK analyses will include Levosimendan and the metabolites, OR-1855 and OR-1896) All blood laboratory test collections must be performed prior to study drug dosing (where other exclusions do not apply). Blood specimens for hematology and serum chemistry will be collected, and results obtained by local laboratories, except for the pharmacokinetic and genotyping samples. These samples will be sent to external labs for analysis of Levosimendan, OR-1855 and OR-1896 metabolites.

14. ATTACHMENTS

14.1 ATTACHMENT 1: Study Drug Dose and Dosing Table

Preparation of the infusion

Levosimendan/placebo infusion for the 24-hour infusion (±30 min) is prepared as follows:

1) for subjects < 85 kg by adding one (1) 5 mL vial of levosimendan/placebo infusion concentrate to one 250 mL infusion bag or bottle of 5% Dextrose or 0.9% Normal Saline.

2) for subjects ≥ 85 kg by adding two (2) 5 mL vials of levosimendan/placebo infusion concentrate to one 500 mL infusion bag or bottle of 5% Dextrose or 0.9% Normal Saline.

The concentration of the diluted infusion is about 50 µg/mL (12.5mg/255mL in a 250mL bag; 25mg/510mL in a 500mL bag).

The diluted infusion is administered intravenously by a peripheral or central route. No other treatments should be administered via the same line.

The dosing regimen

1) During the Lead-In Phase, a continuous infusion of 0.10 µg/kg/min is administered over 24 hours (±30)

2) During Weeks 2 and 3, a continuous infusion of 0.075 µg/kg/min is administered over 24 hours (±30)

3) During Weeks 4 and 5, a continuous infusion of 0.10 µg/kg/min is administered over 24 hours (±30)

On completion of the 24-hour infusion period, the study drug infusion is switched off abruptly.

Placebo is diluted and infused intravenously according to the same schedule as levosimendan.

Infusion Rates

The table below provides detailed infusion rates (for given subject weight as mL/h) for the different infusion rates of a 50 µg/mL preparation of levosimendan/placebo infusion.

Patient's weight (kg)	Infusion rate (mL/h)		
	0.10 µg/kg/min	0.075 µg/kg/min	0.05 µg/kg/min
40-44	5	4	2
45-49	5	4	3
50-54	6	5	3
55-59	7	5	3
60-64	7	6	4
65-69	8	6	4
70-74	8	7	4
75-79	9	7	5
80-84	10	8	5
85-89	10	8	5
90-94	11	8	5
95-99	11	9	6
100-104	12	9	6
105-109	13	10	6
110-114	13	10	7
115-119	14	11	7
120-124	14	11	7
125-129	15	12	8
130-134	16	12	8
135-139	16	13	8
140-144	17	13	8
145-149	17	13	9
150-154	18	14	9
155-159	19	14	9
160-164	19	15	10
165-169	20	15	10

Example for calculating infusion rates if weight is not indicated on the table above:

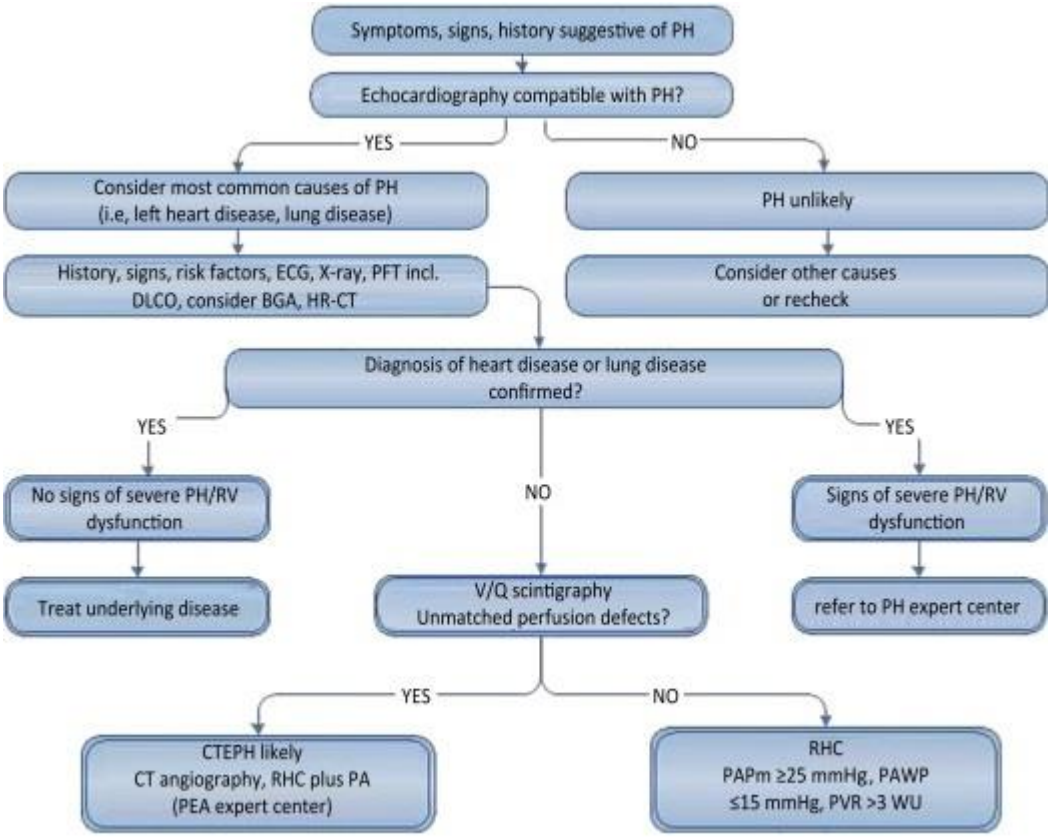
- For a subject weighing 38 kg subject:
- µg/kg/min infusion rate: 0.1 x 38 ÷ 50 x 60 = 5 mL/h
- 0.075 µg/kg/min infusion rate: 0.075 x 38 ÷ 50 x 60 = 3 mL/h

Dose reductions:

Patients receiving 0.10 µg/kg/min should be reduced to 0.075 µg/kg/min and patients receiving 0.075 µg/kg/min should be reduced to 0.05 µg/kg/min. Reductions below 0.05 µg/kg/min are not permitted.

14.2 ATTACHMENT 2: Diagnosis of Pulmonary Hypertension

To be considered for inclusion into this trial, all patients presenting with PH must have undergone a clinical evaluation to determine the etiology, based on the WHO Clinical Classification (52) as outlined in the figure below.



14.3 ATTACHMENT 3: Child-Pugh Classification

Scoring System

The score employs five clinical measures of liver disease.[1] Each measure is scored 1-3, with 3 indicating most severe derangement.

Measure	1 point	2 points	3 points
Total bilirubin µmol/l (mg/dl)	<34 (≤2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/l	>35	28-35	<28
PT INR	<1.7	1.71-2.30	> 2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Different textbooks and publications use different measures. Some older reference works substitute PT prolongation for INR.

In primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC), the bilirubin references are changed to reflect the fact that these diseases feature high conjugated bilirubin levels. The upper limit for 1 point is 68 µmol/l (4 mg/dl), and the upper limit for 2 points is 170 µmol/l (10 mg/dl).

Classification designation

Chronic liver disease is classified as Child-Pugh class A to C, employing the added score from above.

Points	Class
5-6	A
7-9	B
10-15	C

Reference

1. Pugh RN et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973; 60(8):646-9.

14.4 ATTACHMENT 4: Likert Scale

Since starting the medication, please rate the symptoms listed below by circling your choice:	Much Worse	Somewhat Worse	No Different	Somewhat Better	Much Better
1. Shortness of breath	1	2	3	4	5
2. Fatigue/tiredness	1	2	3	4	5
3. Swelling in ankles or legs	1	2	3	4	5
4. Walking upstairs or up hill	1	2	3	4	5
5. Ability to do daily activities	1	2	3	4	5
6. Overall sense of well being	1	2	3	4	5

14.5 ATTACHMENT 5: Cardiac Event Recommendations and Management

Changes in BP or HR that could represent a significant safety concern should be reported to the treating physician (24-hour medical hotline).

If the subject meets any of the dose-limiting event criteria (see section 7.5.4), the following actions on study drug infusion should be undertaken:

1. Blood pressure (systolic) management **prior to enrollment**
    a. Minimum allowed BP 100 mmHg systolic
        i. If <120 on antihypertensive meds, recommend reduce or discontinue
        ii. If >120 on antihypertensive meds, no change.
2. Low blood pressure (systolic <100) management **during trial without symptoms**
    a. On diuretics
        i. With edema = no change
        ii. No edema = reduce or withdraw
    b. On antihypertensive meds
        i. Reduce/withdraw
    c. On no diuretics or antihypertensive meds
        i. No symptoms = observe
        ii. BP <90 = reduce levosimendan/placebo dose
3. **Symptomatic** low BP management
    a. Follow recommendations of asymptomatic scenario (above), **and**
        i. BP <100 mild symptoms = levosimendan/placebo dose reduction
        ii. BP <100 severe symptoms = IV phenylephrine and levosimendan/placebo dose reduction
        iii. BP <90 on lowest dose = discontinue study
4. Sinus tachycardia at rest during the infusion
    a. HR >110 = repeat three times per protocol and obtain BP to validate
    b. HR >110 without symptoms = in the absence of hypotension (above), observe
    c. HR >110 with symptoms of worsening dyspnea in the absence of hypotension (above) = levosimendan/placebo dose reduction
    d. HR >120 (validated) without symptoms = obtain EKG do determine if sinus tachycardia or atrial-fibrillation. *(If HR>120 during the weekly home infusion, the treating physician who is available 24 hours.)*
        i. If sinus tachycardia = levosimendan/placebo dose reduction or withdraw
        ii. If atrial fibrillation = heart rate drug management
    e. Persistent HR>120 despite any/all above measures = discontinue study

14.6 ATTACHMENT 6: Procedure for Right Heart Catheterization at Rest and With Exercise

1. A venous sheath will be placed in the jugular vein percutaneously under ultrasonic imaging guidance.
2. A Swan-Ganz catheter will be inserted and advanced into the pulmonary artery with measurements of the mean RA pressure and RV systolic and diastolic pressures.
3. When the catheter is in the pulmonary artery, the following hemodynamic measures will be recorded after 5 minutes of stabilization:

    - Heart Rate
    - Cuff blood pressure
    - Pulse oximetry
    - PA pressure at end expiration (systolic, diastolic, mean)
    - Mean PCWP at end expiration
    - Thermodilution cardiac output
    - PA oxygen saturation

4. The patient will have their legs placed on the bicycle ergometer in the resting position with a repeat of the following hemodynamic measures after 5 minutes of stabilization:

    - Heart Rate
    - Cuff blood pressure
    - Pulse oximetry
    - PA pressure at end expiration (systolic, diastolic, mean)
    - Mean PCWP at end expiration
    - Thermodilution cardiac output
    - PA oxygen saturation

5. Supine bicycle exercise will be conducted at 25 watts, with the duration of the exercise recorded and noted. The patient will be instructed to pedal at 60 rpm. A final measurement will be made after 3 minutes of steady state exercise which will include the following:

    - Heart Rate
    - Cuff blood pressure
    - Pulse oximetry
    - PA pressure at end expiration (systolic, diastolic, mean)
    - Mean PCWP at end expiration
    - Thermodilution cardiac output
    - PA oxygen saturation

NOTE: For patients who develop such dyspnea that they feel unable to continue the entire 3 minutes, the final hemodynamic measurements will be made at such time and noted. The 24-hour follow-up study, and the Week 6 follow-up study will also be made at the same time interval, even if the patient does not develop dyspnea.

Any deviation from this procedure requires prior approval from the Sponsor.