PROTOCOL: TNX-LVO-05

TITLE: An Open-Label Rollover Study of Levosimendan in Patients with Pulmonary Hypertension with Heart Failure and Preserved Left Ventricular Ejection Fraction (PH-HFpEF)

NCT Number: NCT03624010

Document Approval: 04 June 2021

***Note:** There is an error on the title page of the protocol. The NCT Number referenced (NCT03541603) is of the parent study. The correct NCT Number is NCT03624010 as documented in this cover page.

PROTOCOL: TNX-LVO-05

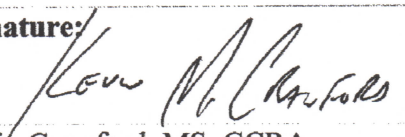
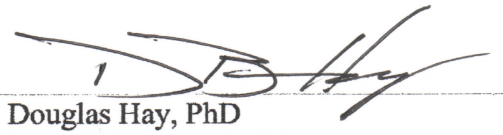
TITLE:	**An Open-Label Rollover Study of Levosimendan in Patients with Pulmonary Hypertension with Heart Failure and Preserved Left Ventricular Ejection Fraction (PH-HFpEF)**
DRUG:	Levosimendan
IND:	IND 47,025
NCT NUMBER:	NCT03541603
SPONSOR*:	Tenax Therapeutics, Inc. One Copley Parkway Suite 490 Morrisville, NC 27560 info@tenaxthera.com
PROTOCOL VERSION AND DATE:	Version 4.1, 04 June 2021

*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:** 07 JUNE 2021
Kevin Crawford, MS, CCRA Director, Clinical Operations Tenax Therapeutics, Inc.	
Signature: 	**Date:** 7 June 2021
Douglas Hay, PhD SVP, Regulatory Affairs Tenax Therapeutics, Inc.	

Principal Investigator's Approval

Signature: 	**Date:** 7 June 2021
Stuart Rich, MD Chief Medical Officer Tenax Therapeutics, Inc.	

Investigator's Acknowledgement

I have read this protocol no. TNX-LVO-05 (Version 4.1)

Title: An Open-Label Rollover Study of Levosimendan in Patients with Pulmonary Hypertension 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 Harmonisation 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/D	6-minute walk test/distance
AE	adverse event
ANCOVA	analysis of covariance
BA	bioavailability
BE	Bioequivalence
BID	Twice daily
BMI	body mass index
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CK	Creatine kinase
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CRA	Clinical Research Associate
eCRF	Case Report Form
CRO	Contract Research Organization
eCRF	electronic case report form
eGRF	estimated glomerular filtration rate
ECG	electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCG	human chorionic gonadotropin
HFpEF	heart failure with preserved ejection fraction
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intention-to-treat
IV	intravenous
IWRS	Interactive Web Response System

LNH	Low, Normal, High
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency (UK)
NDA	New Drug Application
PD	Pharmacodynamic
PH	Pulmonary hypertension
PK	pharmacokinetic
PP	per-protocol
QD	once daily
QID	Four times daily
QoL	quality of life
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SmPC	Summary of Product Characteristics
TAPSE	Tricuspid annular plane systolic excursion
TID	Three times daily
$t_{½}$	apparent terminal-phase disposition half-life
t_{max}	time to maximum plasma concentration
TMF	Trial Master File
WBC	white blood cell
λ_z	apparent terminal-phase disposition rate constant

STUDY SYNOPSIS

Sponsor/Company Tenax Therapeutics, Inc.		
Finished product: Oral levosimendan		
Active ingredient: (-)-(R)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono] propanedinitrile		
Study code: TNX-LVO-05	**Date: Version 4.1 04 June 2021**	
Study title: An Open-Label Rollover Study of Levosimendan in Patients with Pulmonary Hypertension with Heart Failure and Preserved Left Ventricular Ejection Fraction (PH-HFpEF)		
Investigators and study centers: Centers previously performing study with levosimendan		
Objectives: To continue treatment levosimendan in patients who were participating in a Tenax sponsored study after completion of the parent study. Protocol Version 4.1 provides for the transition of patients receiving weekly IV levosimendan to daily oral levosimendan, providing the potential for convenience, more stable dosing, and less risk of infection.		
Methodology: This open-label rollover study is designed to allow patients to continue levosimendan treatment if the patient has tolerated treatment in a clinical study sponsored by Tenax Therapeutics Inc. (the parent study) and if, in the opinion of the Investigator, the patient may benefit from continued levosimendan treatment. Patient safety will be evaluated in accordance with institutional standards of care.		
Sample size: All patients completing the parent study and in the opinion of the Investigator, may benefit from continued treatment.		
Diagnosis and main criteria for inclusion and exclusion: Patients must meet the following criteria to be enrolled in the study: Inclusion Criteria: 1. Provide a personally signed and dated informed consent document prior to initiation of any study-related procedures that are not considered standard of care. 2. Completed double-blind therapy in a PH-HFpEF clinical study sponsored by Tenax Therapeutics, Inc		

3. May, in the opinion of the Investigator, benefit from continued levosimendan treatment.
4. Female patients of childbearing potential must agree to use a highly effective method of contraception.
5. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

Exclusion Criteria:

1. Discontinued treatment in the parent study for any reason other than study completion or Sponsor termination of the study.
2. Pregnant or breastfeeding women.
3. Local access to commercially available levosimendan
4. Inability to comply with planned study procedures
5. Patients with scheduled lung or heart transplant or cardiac surgery
6. Dialysis developed since enrollment in parent study (either hemodialysis, peritoneal dialysis, continuous venovenous hemofiltration, or ultrafiltration)
7. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m2
8. Liver dysfunction with Child Pugh Class B or C (see Attachment 1)
9. Evidence of systemic bacterial, systemic fungal, or viral infection refractory to treatment
10. Weight > 150kg
11. Systolic blood pressure (SBP) cannot be managed to ensure SBP > 100 mmHg at initiation of study drug
12. Heart rate >100 bpm with study drug, persistent for at least 10 minutes at screening.
13. Hemoglobin < 80 g/L
14. Serum potassium < 3.0 mmol/L or > 5.5 mmol/L at baseline that is unresponsive to management.

Investigational product, dose, and mode of administration:

Patients will receive levosimendan at the same dose and schedule they were administered at the conclusion of the parent study. Ongoing patients will be transitioned from weekly IV levosimendan administration to daily oral levosimendan administration up to 4 mg, as tolerated, for the remainder of the study.

Duration of treatment: Patients will continue receiving levosimendan in this Open-Label Extension Study, TNX-LVO-05, and continue in the study for 3 years following transition to oral levosimendan or termination of the trial by the patient or physician decision.

Criteria for Evaluation: Primary Endpoint: • Incidence and severity of adverse events (AEs), clinical laboratory tests (hematology, chemistry), physical examination, vital signs (blood pressure [BP] and pulse rate [PR]) and 12-lead electrocardiogram (ECG) values. Secondary Endpoints: Assessed at Weeks 3, 6, 12, 24, 48, and yearly through Follow-up/termination visit: • 6-minute walk test (6MWT) • Patient global assessment (Kansas City Cardiomyopathy Questionnaire (KCCQ) instrument) • Physician's Assessment of Functional Class • Clinical Events: Death and hospitalizations
Evaluation and statistical methods: Safety and efficacy data will be summarized using descriptive statistics. Formal statistical comparisons will not be performed.

TIME AND EVENTS SCHEDULE

Procedure or Assessment	Ongoing Protocol	Levosimendan IV to Oral Transition[10]					Ongoing Protocol[11]	
	Final Visit in Parent Study	Week 0[1]	Week 2[1,5]	Week 4[1,5]	Final Visit, Week 6[1,4]	Patients titrated at Week 6 should return on Week 8	Office Visits[5] (Weeks 3, 6, 12, 24, 48 and yearly) since enrolling in study	Follow-up Visit (termination visit)
Informed Consent	X	X						
Confirm Eligibility Criteria	X							
Physical Examination	X	X			X[6]	X		X
Body Weight	X	X					X	X
Serum Chemistry and Hematology (Local Lab)[7]	X	X			X[6]	X	X	X
Child Pugh Class[7]	X							X
Vital Signs	X	X	X	X	X	X	X	X
Pharmacokinetic Sample		X[2]		X	X[2]	X[2]		
Electrocardiogram (ECG)	X	X			X[6]	X		X
Levosimendan Administration (oral) / Dose Titration[3]		X	X	X	X[4]			
NYHA Functional Class	X	X			X[6]	X	X	X
6 - Minute Walk Test	X	X			X[6]	X	X	X
Adverse Events/SAEs[8]	X	X	X	X	X	X	X	X
Concomitant procedures and medications	X	X	X	X	X	X	X	X
KCCQ Assessment[9]	X	X			X[6]	X	X	X

Footnotes for Time and Events Schedule

1. Visits will be scheduled 7-9 days following completion of the levosimendan IV dose and every 14 days through the oral levosimendan transition (+/- 48 hrs); at the Investigator's discretion, Week 2 and 4 visits may be performed remotely.
2. Blood sample to be taken prior to the patient's daily dose of oral levosimendan.
3. The first dose of oral levosimendan to be taken 7-9 days after the patient's final weekly IV levosimendan dose. Once oral levosimendan begins, subjects must completely discontinue weekly levosimendan infusions. Patients will begin a daily dose regimen of 1mg daily and titrated at 1mg increments every 2 weeks, as tolerated.
4. At the investigator's discretion, patients that have not demonstrated an adequate response to drug therapy and a tolerance to the 1mg levosimendan TID may be titrated to 1mg QID. Patients that have not tolerated 1 mg levosimendan TID should be down titrated to 1mg BID. All patients that are titrated at Week 6 should return for a Week 8 visit.
5. Due to the COVID-19 pandemic, the investigator may have a phone conversation with the patient rather than having the patient come in for an office visit. The phone conversation should include the following, as reported by the patient; adverse events, concomitant medications (new or changed), concomitant procedures, and blood pressure & heart rate (use provided home blood pressure cuff).
6. If a patient is up or down titrated and therefore scheduled for a Week 8 visit, these procedures do not need to be performed at Week 6.
7. Local labs will be drawn (including NT-proBNP). Child-Pugh Class is only required for patients with documented liver disease.
8. During routine visits and throughout a participation in the study, patients should be queried for any new or changes to AEs, concomitant medications, concomitant procedures, hospitalizations, and/or emergency room visits
9. The KCCQ should be reviewed as soon as possible after the patient completes the questionnaire to ensure all questions have been answered. The patient should be given the appropriate time to complete the questionnaire and to ask any questions they may have.
10. These visits only pertain to patients who have consented to the transition from IV to oral levosimendan.
11. All patients will continue to follow the Ongoing Protocol Assessments. For patients who are on IV levosimendan, these visits will resume for two years based on the date the patient originally entered the TNX-LVO-05 study (e.g., the final visit in the parent study, TNX-LVO-04)

1. BACKGROUND INFORMATION

1.1 Transition from Weekly IV Levosimendan to Daily Oral Levosimendan Regimen

Tenax has recently licensed oral levosimendan from the Orion Corporation. The availability of an oral levosimendan capsule provides a convenient alternative to the weekly 24hr IV levosimendan in this study. Importantly, the safety concerns of local and systemic infections associated with IV administration through a PICC line or port-a-cath administration can be avoided. This protocol amendment identifies the procedures that will be used in transitioning consenting patients to a daily oral levosimendan dose regimen.

Patients that do not consent to this amendment will continue in the study on IV levosimendan. These patients will continue treatment until two years from the date of entry into the TNX-LVO-05 study (i.e., the final visit in the parent study, TNX-LVO-04), at which time they will be discontinued.

Numerous completed studies of oral levosimendan using immediate-release capsules provide a rich database of PK data (levosimendan and metabolites OR-1855 and OR-1896) in healthy volunteers and heart failure patients. These studies are listed in the updated Investigator's Brochure. Notably, Orion performed the PERSIST study in ~300 CHF patients receiving oral levosimendan at 1mg QD, 1mg BID, or placebo for 6 months.

1.2 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 treatment of PH-HFpEF subjects acknowledge that the accepted treatment target is 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)

1.3 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). Over 1.8 million subjects have been treated with levosimendan worldwide by the end of December 2019.

A more 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).

1.3.1 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)

1.3.2 **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 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.

1.3.3 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 8 weeks. Similar responses were observed in the mPAP of subjects 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).

1.3.4 Chronic oral levosimendan treatment in severe heart failure (PERSIST)

PERSIST was a randomised, double-blind, multi-centre, phase II study, where 2 doses of oral levosimendan were compared with placebo in 307 patients with severe CHF (NYHA functional class IIIb-IV). The patients received either 1 mg of levosimendan once daily (102 patients), 1 mg of levosimendan twice daily (103 patients), or placebo (102 patients) as add-on therapy for at least 180 days (53, 54).

The primary endpoint of the study was an exploratory composite (called 'Patient Journey'), consisting of repeated patient's symptom assessments, worsening heart failure events and all-cause mortality during the first 60 days. Additionally, Minnesota Living with Heart Failure QoL score (MLHFQoL) and plasma NT-pro-BNP concentration were assessed repeatedly.

Patients assigned to the lower dose of levosimendan had more severe CHF at baseline, as suggested by a higher median NT-pro-BNP concentration, more hospitalizations within the previous 12 months, and the highest furosemide (or equivalent) dose at baseline. The steady-state concentration of the active metabolite OR-1896 was 2.7 and 4.3 ng/ml in the lower and higher levosimendan group, respectively.

There were no differences in symptoms, worsening heart failure events, and death between the pooled levosimendan and placebo groups, resulting in a similar Patient Journey score during the 60 days after randomization ($p = 0.567$). However, the number of worsening heart failure events decreased with levosimendan, but the difference compared to placebo was not statistically significant.

There was a decrease (= improvement) in the MLHFQoL score during the study in all groups. When the levosimendan groups were pooled, a net benefit of 3-4 points over placebo was seen with levosimendan ($p < 0.001$). A substantial and persistent reduction of 30-40% was seen in NT-pro-BNP in both levosimendan groups, while no change was observed with placebo ($p < 0.001$).

No differences were observed in time to death or worsening heart failure, all-cause and cardiovascular mortality, and number of days alive and out of hospital between the pooled levosimendan groups and placebo. Mortality was numerically higher in levosimendan treated patients: 15, 8, and 6 patients died in the levosimendan 1 mg, levosimendan 2 mg, and placebo groups, respectively. There was no clear pattern to the excess mortality and in particular no evidence of an increase in arrhythmias. The low overall mortality and the fact that the highest number of deaths was seen with the lower levosimendan dose, which also had the most severe heart failure at baseline, suggest that chance may have played an important role in distribution of deaths. The QTc interval (Fridericia) was virtually unchanged and similar in all treatment groups. HR increased by 7-8 bpm in both levosimendan groups, while it was unchanged with placebo ($p < 0.0001$). The changes in BP were modest; mean decrease in systolic BP was maximally 2.5 mmHg in the placebo group and 1.8 mmHg and 0.6 mmHg in the lower and higher levosimendan dose groups, respectively.

The most common AE was cardiac failure, which was reported numerically more often in the placebo group. Ventricular tachycardia or fibrillation was reported in 1, 2 and 6 patients in the levosimendan 1 mg, levosimendan 2 mg, and placebo groups, respectively.

Renal function seemed to improve in levosimendan-treated patients, as suggested by a greater increase in creatinine clearance in the pooled levosimendan group compared with placebo ($p < 0.001$).

In conclusion, this study failed to show a beneficial effect of levosimendan on a novel and unvalidated composite primary endpoint (the Patient Journey), but improvements were observed in QoL score, renal function, and reductions in NT-pro-BNP. Interpretation of the results may have been confounded by baseline imbalances in the severity of heart failure.

1.3.5 Weekly Intravenous Levosimendan Treatment in Pulmonary Hypertension with Heart Failure and Preserved Ejection Fraction (PH-HFpEF)

Levosimendan was studied in a Phase 2 double-blind clinical study of PH-HFpEF patients (HELP Study, TNX-LVO-04) that tested the effects of once-weekly intravenous levosimendan on patient's hemodynamics and 6-minute walk distance. Patients were required to have evidence of moderate-to-severe pulmonary hypertension defined hemodynamically by a pulmonary artery pressure (mPAP ≥35 mmHg), a pulmonary capillary wedge pressure (PCWP >20 mmHg), LVEF ≥40% and NYHA II-III).

The study was conducted in two phases. The Lead-in Phase (open-label) consisted of a right heart catheter at baseline including invasive hemodynamic measurements at rest, legs up, and supine bicycle exercise (25 watts). All patients then received a 24-hour (±30 min) infusion of levosimendan (0.10 μg/kg/min) followed by a repeat right heart catheter and hemodynamic measurements. To proceed to the Chronic Phase, patients were required to be considered a levosimendan "responder", defined as exhibiting a ≥4 mmHg reduction of PCWP at during exercise at 25 Watts with no more than a 10% decrease of cardiac index. Responders were randomized to receive once weekly outpatient infusions of levosimendan or placebo. Patients underwent a final right heart catheter with invasive hemodynamic assessments at the final visit (Week 6). All hemodynamic data were read by an independent reviewer, blinded to study treatment. These data were used in the final analysis of the study. Of 44 subjects enrolled, 37 (84%) qualified as responders and were randomized to levosimendan (n=18) or placebo (n=19). Patients (69±9 years old, 61% women) displayed severe combined pre- and post-capillary PH at baseline (resting mPAP 41±9, exercise PCWP 37±11 mmHg).

Levosimendan was shown to be safe and effective which represents the first evidence of drug-related improvements in both hemodynamic and clinical endpoints in patients with PH-HFpEF. At Week 6, levosimendan-treated patients had significant reductions in PCWP versus baseline at rest and with legs up (-5.10 mmHg, p=0.0006 and -6.00 mmHg, p=0.0007, respectively). The effect on PCWP with 25 watts exercise versus baseline compared to placebo, the primary endpoint, was not significant (-1.40 mmHg, 95% CI, -7.7 to 4.8, p=0.65). However, in a mixed-

effect repeated measure regression analysis incorporating all test conditions (rest, legs up, and exercise), levosimendan reduced PCWP by 3.9±2.0 mmHg as compared to placebo (p=0.047).

Importantly, levosimendan-treatment resulted in significant reductions in resting mPAP and RAP, two hemodynamic measures that have been shown to be highly correlated with mortality in PH patients. The change from baseline to Week 6 in mPAP and RAP measured at rest was -5.43 mmHg, p=0.0003 and -4.50 mmHg, p=0.0004, respectively. These hemodynamic effects appear the result of K-ATP activation and independent of the drug's inotropic activity, as the CI f levosimendan-treated patients was unchanged. A detailed analysis of the mechanism of action looking at noninvasive pressure/volume relationships did not demonstrate any inotropic effects following the initial 24-hour infusion of levosimendan. Rather, the data support that effects on the estimated stress blood volume may be important.

Patients receiving levosimendan also had a statistically significant, and clinically significant, improvement in exercise capacity over placebo as measured by their 6MWD (29.3 meters (2.5, 56.1 95%CI) p=0.0329. 6MWD did not differ at baseline but decreased by an average of -12.7 meters in the placebo group and increased by an average of 16.6 in the levosimendan.

1.3.6 **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 is in contrast to the laboratory safety variable analyses; in IV studies decreases in hemoglobin and serum potassium have been consistently reported (29, 47).

There have been 8 studies of oral levosimendan in HF patients, including 368 levosimendan treated patients. The most frequently reported AEs in cardiac patients in all oral levosimendan studies versus placebo were headache (13.3% vs. 2.3%) and cardiac failure (12.0% vs. 15.9%) followed by increased HR (7.6% vs. 1.7%), tachycardia (6.5% vs. 6.8%), palpitations (6.5% vs. 0.6%), dizziness (6.3% vs. 4.5%) and hypotension (6.0% vs. 3.4%).

In legacy 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 the Phase 2 HELP Study in PH-HFpEF patients levosimendan was well-tolerated with adverse events limited to generally mild events known to be associated with the drug (e.g. headache, tachycardia) and events related to the disease (e.g. dyspnea, cardiac failure). Serious adverse events were few, including infusion-related infection and events expected in the population (cardiac failure).

No patients were discontinued due to increased heart rate or hypotension. One patient discontinued with moderate palpitations on Day 4 following their open label levosimendan IV administration. The patient had atrial fibrillation, non-sustained supraventricular tachycardia accelerated junctional tachycardia at baseline.

The low dose and modest rate of levosimendan infusion regimen (0.075-0.1µg/kg/minute for 24 hours weekly without initial bolus) was safe with no concerns of hypotension after the initial dose. Cardiac monitoring at baseline and Week 5 demonstrated the cardiac safety of a weekly IV infusion of levosimendan at doses up to 0.10 µg/kg/minute for 24 hours. The weekly low

levosimendan dose over an extended 24-hour infusion produced no signal of arrhythmias; increased atrial fibrillation, sustained atrial tachycardias, symptomatic atrial arrythmias of any kind, sustained monomorphic ventricular tachycardias, Symptomatic ventricular arrhythmias of any kind, of ventricular fibrillation.

In marketed use, over 1.8 million subjects worldwide have been treated with Simdax® (levosimendan) injection. The most commonly reported adverse reactions in the adverse drug reaction reports received from health care 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).

1.3.7 Rationale for Chronic Oral Levosimendan

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

- Levosimendan is 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).
- In the Phase 2 HELP Study in PH-HFpEF patients, levosimendan promoted vasodilation and peripheral perfusion, reduced pulmonary capillary wedge pressure (PCWP) pulmonary arterial pressure (PAP) and right atrial pressure (RAP), and enhanced exercise capacity.
- In the Phase 2 HELP Study in PH-HFpEF patients, levosimendan promoted vasodilation and peripheral perfusion, reduced pulmonary capillary wedge pressure (PCWP) pulmonary arterial pressure (PAP) and right atrial pressure (RAP), and enhanced exercise capacity. These positive effects of levosimendan may be due to levosimendan's ability to increase venous capacitance and reduce stressed blood volume (55).
- Oral daily dosing of levosimendan will result in more stable blood levels of the active metabolite OR-1896 which is responsible for the chronic efficacy.
- Similar improvements in cardiovascular hemodynamics have been seen in studies that evaluated oral dosing of levosimendan in HFrEF patients.

- A single dose study comparing levosimendan IV vs Oral Administration was conducted by Harjola et al. This study found that single oral doses of levosimendan (1mg, 2mg, and 4 mg) generally produced similar hemodynamic effects seen with comparable IV bolus doses (56)

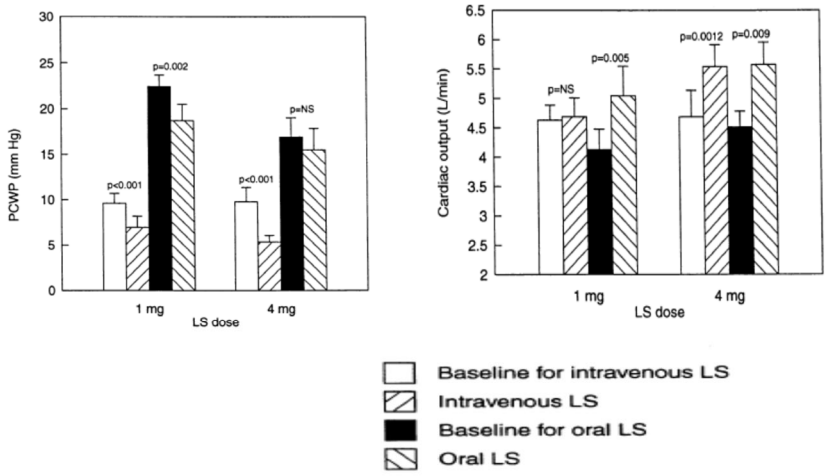

FIGURE 1. Pulmonary capillary wedge pressure (PCWP) and cardiac output in patients receiving intravenous (n = 12) and oral (n = 10) doses of 1 mg and 4 mg of levosimendan (LS) in 2 different studies. Baseline values and maximum responses are shown (mean ± SEM). The p-values refer to the difference between maximum response and respective baseline value. NS = not significant.

- A sub-study of the PERSIST trial was conducted (Jalanko et al) evaluated hemodynamic changes seen following chronic daily doses of 1mg and 2mg levosimendan. Favorable changes in PCWP and BNP were observed following 90and 180 days of daily oral administration (57)

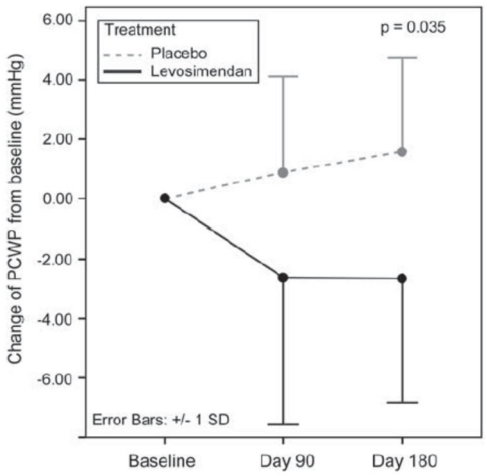

Figure 2. Change of echocardiographic PCWP from baseline to day 180 in placebo and levosimendan treated patients analysed by repeated measures ANOVA (p = 0.035).

Table III. Follow-up.

	Baseline	Day 90	Day 180
PCWP (mmHg)			
Placebo	15.9 (5.7)	16.6 (5.5)	17.3 (5.7)
Levosimendan	18.8 (6.1)	16.4 (6.2)	16.4 (5.4)*
HR (bpm)			
Placebo	74 (14)	72 (10)	72 (11)
Levosimendan	73 (10)	78 (12)	81 (12)
SBP (mmHg)			
Placebo	127 (15)	126 (22)	130 (18)
Levosimendan	121 (15)	129 (14)	127 (19)
LVEDD (mm)			
Placebo	66 (8)	66 (8)	67 (7)
Levosimendan	66 (9)	65 (9)	65 (9)
LVEDV (ml)			
Placebo	188 (63)	189 (59)	197 (64)
Levosimendan	211 (72)	196 (64)	205 (75)
LVEF (%)			
Placebo	25% (8)	28% (10)	25% (10)
Levosimendan	25% (5)	26% (8)	26% (7)

Values presented as mean (±SD).
*p = 0.035 for difference between groups.

1.3.8 Target Plasma Concentrations of OR-1896 in chronic treatment of PH-HFpEF Patients

Levosimendan represents an active prodrug to the active metabolite OR-1896 with extended pharmacodynamic 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 chronically active moiety of levosimendan administration is the metabolite OR-1896. Levosimendan is cleared within 5 hours of ending an infusion.

The wide range of OR-1896 concentrations observed in daily oral levosimendan dosing (PERSIST study, see Section 1.3.4) and weekly IV administration (HELP Study, Section 1.3.5) precludes the identification of a specific oral dose to be used in the IV to oral transition. Importantly, the range of OR-1896 plasma concentrations observed in the PERSIST study of class IIIb-IV CHF patients overlap those observed in the HELP Study of PH-HFpEF patients (Figure 3).

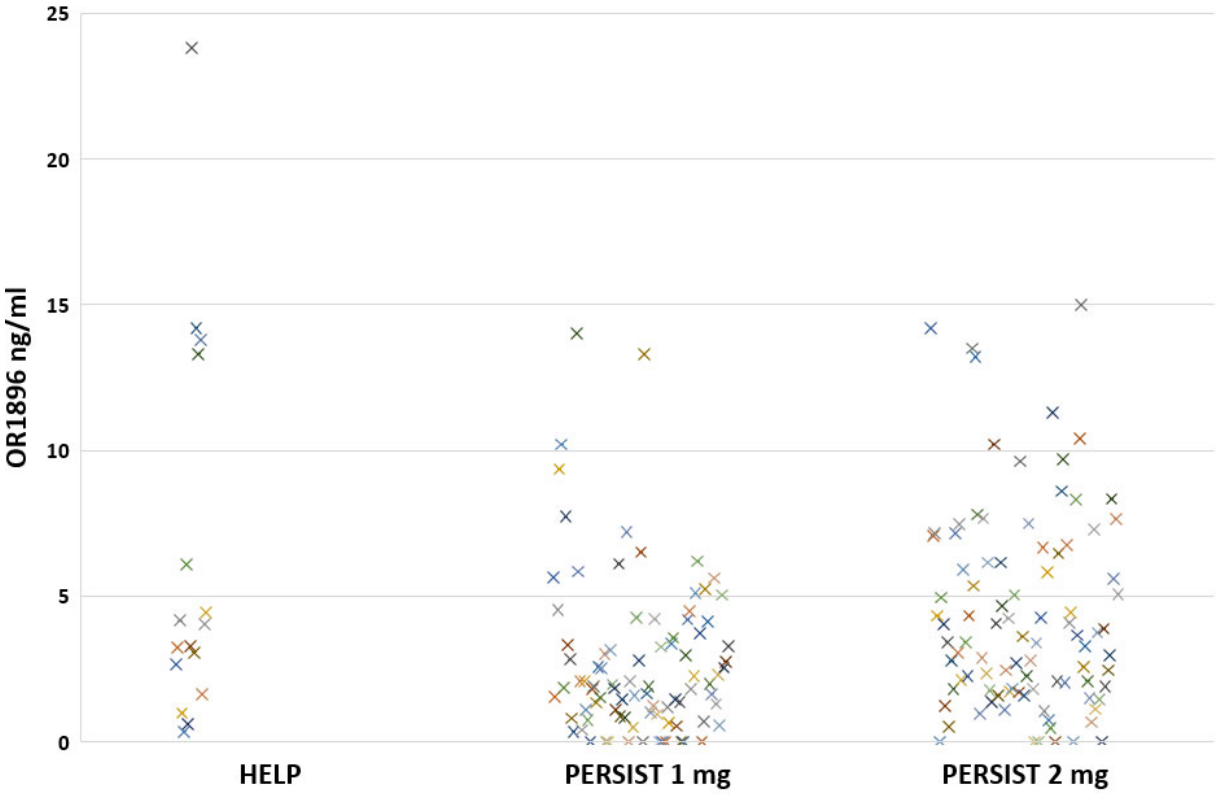

Figure 3. Comparison of OR-1896 Plasma Concentrations in PERSIST Study of Daily Oral Levosimendan (1mg QD, 1 mg BID) versus the HELP Study of Weekly IV Levosimendan (0.1 ug/kg/min for 24 hrs).

However, only one third of the HELP Study patients were sampled at peak OR-1896 levels, 2-3 days following their previous levosimendan IV dose. The remaining patients were sampled beyond the period of peak OR-1896 concentrations observed in a weekly IV levosimendan regimen. An opportunity to titrate patients to 4 mg total daily dose (1mg QID), as tolerated based on blood pressure and heart rate, will ensure all transitioning patients will achieve adequate steady state levels of OR-1896.

1.3.8.1 IV Levosimendan

OR-1896 concentrations were modeled for the intravenous levosimendan dose regimen of 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 were expected to be between 0.5 ng/mL and 2.5 ng/mL in extended intermittent use.

In the HELP Study, PK samples were collected at the final visit. Generally, the samples were collected 2-8 days after completion of the final levosimendan infusion on Week 5. There was a large range of OR-1896 levels (0.347 to 23.8 ng/mL). Some of the variation is associated with the time since completion of the previous levosimendan dose. Patients returning 2-3 days after their dose tended to have higher plasma concentrations of the metabolites. There were several apparent anomalies in levosimendan, OR-1855 and OR-1896 plasma concentrations which have not been explained, despite an internal audit by the laboratory conducting the analyses. There was no identifiable lower or upper limit of OR-1896 that predicts efficacy as measured by hemodynamic or 6MWD.

1.3.8.2 Oral Levosimendan

Orion performed the PERSIST study in 307 CHF patients receiving oral levosimendan at 1mg QD, 1mg BID, or placebo for 6 months. Levosimendan patients demonstrated substantial reductions in NT-proBNP and dose-related improvement in the Minnesota Living with Heart Failure quality of life score (MLHFQOL). The mean (SD) steady state OR-1896 concentrations were 2.7 (SD 2.8) and 4.3 (SD 3.4) ng/mL at 1mg QD and 1mg BID, respectively on Day 30 and remained consistent through the treatment period.

The plot of OR-1896 concentrations in patients receiving oral levosimendan at 1mg QD or 1mg BID in the PERSIST study overlaps the range of OR-1896 concentrations observed in patients receiving weekly intravenous levosimendan at 0.1 µg/kg/min for 24 hours in the HELP Study of PH-HFpEF patients (Figure 3). OR-1896 concentrations in both studies were highly variable.

1.3.8.3 Individualized Oral Dose Regimen

The broad range of observed OR-1896 concentrations in the HELP and PERSIST studies indicates a personalized daily dose may improve individual patient response to levosimendan and its active metabolite OR-1896. The wide range in plasma levels of OR-1896 observed in the HELP and PERSIST studies indicate steady state concentrations from daily dosing will be somewhat independent of body weight or the severity of CHF. The transition from IV to oral levosimendan provides an opportunity for personalized dosing based on patient tolerability.

The step wise increases from 1mg up to 4mg daily levosimendan doses will be based on tolerability of the therapy. Heart rates and blood pressures will be monitored and recorded by the patient each day. Guidance will be provided to ensure measurements are standardized at rest during the same approximate time each day. Investigators will review the heart rate and blood measure measurements to ensure the patient has tolerated their current levosimendan dose and guide the titration (up or down) according to Attachment 3 Cardiac Event Recommendations and Management and investigator judgment.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

The study will evaluate the safety and efficacy of levosimendan 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.

2.2 Study Objectives

2.2.1 Primary Objectives

This study will evaluate the safety and tolerability of levosimendan in extended use after completion of the parent study.

2.2.2 Secondary Objectives

The study will evaluate whether the effectiveness of intermittent (weekly) levosimendan and daily oral levosimendan (based on patient transition) is sustained in extended use.

2.3 Study Design

This extension study is designed to investigate the safety and efficacy of extended levosimendan in patients who previously received levosimendan in PH-HFpEF study sponsored by Tenax and may, in the investigator's opinion, derive benefit from continued treatment. Patients will be screened for eligibility at the last visit in the treatment period of the parent study. Eligible patients will be enrolled into the study immediately upon confirmation of eligibility so that levosimendan is not interrupted.

Efficacy assessments (6MWT, Patient global assessment (based on the KCCQ instrument), Physician's Assessment of Functional Class, Clinical Events; Death and hospitalizations) will be performed at 3, 6, 12, 24, 48, and yearly through Follow-up/Termination visit. For patients that transition from IV to oral (Week 0 and 6 or 8), the Time and Events Schedule for oral levosimendan should be followed Patients will undergo a Follow-Up Visit (at termination) as soon as possible after study drug discontinuation, but within 2 weeks.

For patients that transition to oral levosimendan, the patient should be instructed to monitor their resting heart rate and blood pressure each day prior to the first dose. The patient should use the home monitoring device (provided at the initiation of the initial levosimendan study) to determine their resting heart rate and blood pressure after being seated at rest for at least 5 minutes. The heart rate and blood pressure readings should be recorded in the diary provided as well as the number of capsules the patient has taken each day. The patient should have their diary ready to review with the investigative site in each communication with the site and at office visits.

Patients whose BP falls below the specified range will be queried regarding any symptoms of hypotension which may result in the down titration of the levosimendan dose.

Patients whose heart rate exceeds the specified range will be queried regarding symptoms of worsening heart failure. An excessive heart rate in a patient with no evidence of worsening heart failure, suggests that the increased heart rate is a direct drug effect requiring adown titration of the levosimendan dose.

2.3.1 Regimen Transition: Weekly Intravenous to Daily Oral Levosimendan

With Version 4.1, current patients may transition from intravenous (IV) levosimendan to oral levosimendan.

All patients that have signed consent will be transitioned from weekly IV levosimendan to daily oral levosimendan over a 6-week period, with visits every 2 weeks.

Unless otherwise noted, patients will continue to visit the investigational site at Weeks 3, 6, 12, 24, 48 and yearly through Follow-Up Visit (at termination) up/Termination visit per the date the patient first started the TNX-LVO-05 study (e.g., completion of the parent study).

2.4 Number and Type of Subjects

Patients who completed all study visits through the end of the parent study were eligible to enroll into the Open-Label extension study.

2.5 Investigational Product

Upon entry into the study, levosimendan was administered in open-label, intravenously at 0.075 µg/kg/min for 24 hours ±30 min, or as per directed by the treating physician. A physician was to assess the patient's safety at Week 3 and up-titrate to 0.1 µg/kg/min for 24 hours. The decision to increase the dose was to be based on the absence of disease or drug related adverse events and the investigator's discretion.

If a subject was down-titrated to 0.05 µg/kg/min in the TNX-LVO-04 study for either the Lead-In dose or during the double-blind portion of the study, the subject was to start at this dose, with the first opportunity to up-titrate following at Week 3.

All subjects will be transitioned to an oral dose of levosimendan once an informed consent form has been signed. Those currently receiving levosimendan IV weekly will return to the investigational site and receive 1mg levosimendan capsule daily for two weeks.

Subjects may then be titrated up every 2 weeks at 1mg levosimendan increments up to maximum of 4 mg daily (1mg QID), based on assessments of safety and patient's clinical response (see Attachment 3 Cardiac Event Recommendations and Management). Patients that tolerate 3 mg (1mg TID) oral levosimendan TID that have not demonstrated a 6MWD equivalent or better than the recorded 6MWD at initiation of their IV to oral levosimendan may be titrated to 4 mg (1mg QID). Patient's that experience identified safety concerns in Attachment 3 should be downtitrated at 1 mg/day increments or discontinued at the physician's discretion.

Once a patient completes the transition to oral levosimendan, all IV drug and ancillary supplies related to the administration of IV levosimendan will be returned to the central pharmacy for destruction.

At the initial visit of the IV to oral levosimendan transition, each patient will receive a supply of 1mg oral levosimendan capsules. Subsequent supplies may be shipped to the patient's home.

2.6 Sites and Regions

This study will be conducted at any site that participated in the parent study and has ongoing patients.

3. STUDY POPULATION

3.1 Inclusion Criteria

Diagnosis and main criteria for inclusion and exclusion:

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

Enrollment Criteria:

1. Provide a personally signed and dated informed consent document prior to initiation of any study-related procedures that are not considered standard of care.
2. Completed double-blind therapy in a PH-HFpEF clinical study sponsored by Tenax Therapeutics, Inc.
3. May, in the opinion of the Investigator, benefit from continued levosimendan treatment.
4. Female patients of childbearing potential must agree to use a highly effective method of contraception.
5. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

3.2 Exclusion Criteria

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

1. Discontinued treatment in the parent study for any reason other than study completion or Sponsor termination of the study.
2. Pregnant or breastfeeding women.
3. Local access to commercially available levosimendan.
4. Inability to comply with planned study procedures
5. Patients with scheduled lung or heart transplant or cardiac surgery
6. Dialysis developed since enrollment in parent study (either hemodialysis, peritoneal dialysis, continuous venovenous hemofiltration, or ultrafiltration)

7. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2
8. Liver dysfunction with Child Pugh Class B or C (see Attachment 1)
9. Evidence of systemic bacterial, systemic fungal, or viral infection refractory to treatment
10. Weight > 150kg
11. Systolic blood pressure (SBP) cannot be managed to ensure SBP ≥ 100 mmHg at initiation of study drug
12. Heart rate ≥ 100 bpm with study drug, persistent for at least 10 minutes at screening.
13. Hemoglobin < 80 g/L
14. Serum potassium < 3.0 mmol/L or > 5.5 mmol/L at baseline that is unresponsive to management

3.3 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

3.4 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 Follow-Up Visit (at termination) evaluations. Comments (spontaneous or elicited) or complaints 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 Case Report Form (eCRF) and source documents.

3.4.1 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

3.4.2 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.

4. PRIOR AND CONCOMITANT TREATMENT

4.1 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.

4.2 Concomitant Treatment

All subjects must be optimally managed on diuretics and oxygen therapy as indicated by the standard of care.

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

4.3 Allocation of Subjects to Treatment

This is an Open-Label extension of the parent study. All patients who enroll into this study received an open-label levosimendan. With the availability of oral levosimendan capsules, all consenting patients in TNX-LVO-05 will be transitioned to daily doses of oral levosimendan and continue in the study for 3 years following transition to oral levosimendan or termination of the trial by the patient or physician decision.

5. INVESTIGATIONAL PRODUCT

5.1 Levosimendan

IV Levosimendan

Levosimendan will be provided to the subjects 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.

Oral Levosimendan

Oral levosimendan will be provided as a single-unit, immediate release, size 3, yellow and grey capsule. Each capsule contains 1mg levosimendan, intended to be released rapidly for absorption from the gastrointestinal tract. In addition to active ingredient, the capsules contain the following excipients, all of which comply with the monographs of the European Pharmacopoeia.

Levosimendan is supplied by the Orion Corporation, Espoo, Finland.

5.2 Packaging

IV Levosimendan

Levosimendan 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.

Oral Levosimendan

Levosimendan will be provided in high-density polyethylene (HDPE)-container closed with HDPE/poly propylene (PP) screw closure.

5.3 Labeling

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

Each container will have appropriate directions for use and other required information.

Drug accountability forms will be used for tracking study drug administration. Information from the container will be included on the subject's drug accountability form to document capsule usage.

5.4 IV Levosimendan (Weekly Infusions)

5.4.1 Dosage and Administration

During the routine weekly infusion, patients will be administered a continuous intravenous (IV) infusion of a standard infusion dose of 0.075 - 0.1 µg/kg/min for 24 hours (±30 min); (levosimendan). The dose may be adjusted by the treating physician as needed (see section 6.4.2). No bolus of study drug will be administered.

Study drug concentrated solution (2.5 mg/mL), levosimendan, will be mixed with diluent and administered as weekly infusions at 0.075 µg/kg/min for 24 hrs. Patients may have a dose escalation at Weeks 3 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 4) or other prohibitive rationale.

If a subject was down-titrated to 0.05 µg/kg/min in the TNX-LVO-04 study for either the Lead-In or during the double-blind portion of the study, the subject should start at this dose, with the first opportunity to up-titrate at Week 3 of the Open-Label Extension Study, TNX-LVO-05.

Note: A patient will be discontinued from the study, if the patient develops a complication or infection associated with the PICC line or port-a-cath that prevents its further use.

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 4 of this protocol before administration of study drug to calculate the appropriate infusion rate based on the subject's body weight.

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.

5.4.2 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.

5.4.3 Storage

Study drug (levosimendan infusion 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.

5.5 Oral Levosimendan

5.5.1 Dosage and Administration

Dosing Regimen: Subjects will start with a 1 mg levosimendan dose (in the morning) for 2 weeks. If tolerated, the dose will be increased after 2 weeks to 1 mg BID, after 4 weeks to 1mg TID, and after 6 weeks (if applicable)[1] to 1mg QID. The titration sequence is as follows:

Previous IV Infusion	Week 0 (Office)	Week 2 (Home)	Week 4 (Home)	Final Visit Week 6 (Office)	Week 8 (Office)

0.10 µg/kg/min	1mg **QD** (1mg total daily dose) *Morning*	1mg **BID** (2mg total daily dose) *Every 12 hrs.*	1mg **TID** (3mg total daily dose) *Every 8 hrs.*	Patient evaluated for further titration (up or down)[1]	Only patients titrated (up or down) at Week 6 *No further dose titration above 4mg QID*

[1] At the investigator's discretion, patients that have not demonstrated an adequate response to drug therapy and a tolerance to the 1mg levosimendan TID may be titrated to 1mg QID. Patients that have not tolerated 1 mg levosimendan TID should be down titrated to 1mg BID. All patients that are titrated at Week 6 should return for a Week 8 visit.

5.5.2 Dose Adjustment

The oral levosimendan dose may be decreased in 1 mg increments 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 date of discontinuation or down titration. Patients should be monitored closely until clinically stable.

Missed doses should be skipped and not taken as a double dose at the next dosing time.

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.

5.5.3 Dose-limiting Events

Dose limiting cardiac events and instructions are detailed in Attachment 3 Cardiac Event Recommendations and Management. 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 levosimendan.

5.5.4 Storage

Study drug (levosimendan capsules) must be stored at room temperature.

The Sponsor must be notified upon discovery of any excursion. 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/consumed by subjects until the impact is determined and product is deemed appropriate for use.

5.6 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.).

5.7 Drug Accountability

Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

Investigational product will be administered only to subjects included in this study following the procedures set out in the study protocol. All dispensing will be documented.

No investigational product stock or returned inventory from a Tenax sponsored study may be removed 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.

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.

5.8 Subject Compliance

Compliance will be monitored throughout the transition period (IV to oral levosimendan) and ongoing throughout the remainder of the study.

6. STUDY PROCEDURES (IV LEVOSIMENDAN)

6.1 Ongoing Weekly Infusions

Weekly visits, occurring approximately every 7 days, should be performed within ±48 hours of the scheduled visit.

6.2 Weeks 3, 6, 12. 24, 48, and yearly, and Follow-Up Visit (at termination) (Office Visits)

Visits at Weeks 48, yearly, and Follow-Up Visit (at termination) should be performed within ±72 hours of the scheduled weekly visit. These visits will be performed at the investigator's office. The Follow-Up Visit (at termination) will be calculated as the earlier of two years from the subject's date of entry into the TNX-LVO-05 Study or as soon as possible after study discontinuation, but within 1 week.

During this visit, the following procedures will be performed:

- Vital signs
- Body Weight (Week 3 only)

- 6MWT
- Quality of Life (QOL) assessment
- NYHA Functional Class
- Physician Assessment
- Assess adverse events
- Concomitant medications and/or procedures

For subjects who discontinue the study early, the same procedures as listed above should be performed.

Adverse events experienced by the patient since the previous visit, should be assessed at any unscheduled visit at the investigator's office.

6.3 Study Evaluations and Procedures

Study procedures will occur according the Time and Events Schedule.

Patients should be instructed to report adverse events associated with their in-home administration of the drug and any concerns that are identified between administration. Each report should be evaluated with respect to the need for an office visit for further assessment of safety.

Any adverse event identified by the patient during unscheduled visits should be recorded and followed, as appropriate, in accordance with Section 7.

6.4

7. STUDY PROCEDURES (IV TO ORAL TRANSITION)

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

Section 6.1 describes the transition of patients from IV to oral levosimendan. Section 6.2 outlines the routine visits that will occur according to the original date the patient entered the TNX-LVO-05 study from the parent study.

During both the transition period (6.1), ongoing visits (6.2), and throughout the duration of the trial, adverse events must be collected according to Good Clinical Practice (GCP). Sites should query the patients for any new adverse events, worsening of adverse events, and changes to or new concomitant medication and/or procedures. The ongoing documentation of blood pressure and heart rate should be maintained in the patient's chart and in the case report form, as applicable.

Attention should be paid to certain safety events and changes in concomitant medications. During ongoing and routine visits, the patient should be asked if they have experienced any of the following changes:

- Palpitations associated with:
  - Shortness of breath
  - Significant lightheadedness
  - Passing out/syncope
- Edema (swelling):
  - Frequency (never, occasionally, constantly)
- Shortness of breath with activity:
  - Frequency (rarely, often, constantly)
- Diuretic use:
  - Changes (increase, no change, decrease)
- Hospitalization or Emergency Room visits

7.1 Treatment Transition: Weekly Intravenous to Daily Oral Levosimendan

All ongoing patients will be transitioned from IV to oral levosimendan over 6 weeks.

Any visit that occurs during the transition period that falls on the same day as a regularly scheduled visit (i.e. Week 3, 6, 12, 24, 48 or yearly) should include all the required procedures for both visits.

The first patient visit will occur 7-9 days following the completion of their last levosimendan infusion. Prior to starting any procedures related to the transitions, patients must sign an updated informed consent form.

Due to the ongoing pandemic (as of the date of this protocol) visits according to the Time and Events Schedule may be modified to accommodate patient scheduling. For example, a visit at transition Week 6 may be extended two additional weeks to accommodate either patient travel or hospital restrictions limiting patient visits.

Following successful transition to oral levosimendan, the port-a-cath should be removed for purposes of this study. During the transition (Weeks 0 to 6 or 8), the port-a-cath should be

maintained by the patient (i.e., flushing) according to the investigational site's institutional practices.

7.1.1 IV-Oral Transition Week 0

During this visit, the following procedures will be performed:

- Vital signs and ECG
- Physical Exam (including body weight)
- 6MWT
- Hematology and chemistry blood samples
- Pharmacokinetic sample
    - The sample should be taken before the patient consumes their first dose of oral levosimendan
- NYHA Functional Class
- Assess adverse events.
- Concomitant medications and/or procedures
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Oral levosimendan

7.1.2 IV-Oral Transition Week 2

During this visit, the following procedures will be performed (this visit may be performed virtually, at the investigator's discretion):

- Vital signs
- Assess adverse events

7.1.3 IV-Oral Transition Week 4

During this visit, the following procedures will be performed (this visit may be performed virtually, at the investigator's discretion):

- Vital signs
- Assess adverse events
- Pharmacokinetic sample
    - *Note: if this visit is performed remotely and a home health nurse is unavailable to draw the PK sample, this sample may be missed*

7.1.4 IV-Oral Transition Week 6 – Final Visit

During this visit, the following procedures will be performed:

- Vital signs and ECG
- Physical Exam
- Hematology and chemistry blood samples
- Assess adverse events
- Pharmacokinetic sample
- 6MWT
- NYHA Functional Class
- Kansas City Cardiomyopathy Questionnaire (KCCQ)

Once a patient transitions to oral levosimendan, all references in this protocol to the administration of IV levosimendan, will no longer apply for that patient. All study drug and ancillary supplies related to the administration of IV levosimendan will be returned to the central pharmacy for destruction.

7.1.5 IV-Oral Transition Week 8

This visit is only required for patients who titrated (up or down) at the Week 6 visit.

During this visit, the following procedures will be performed:

- Vital signs
- Physical Exam
- Hematology and chemistry blood samples
- Assess adverse events
- Pharmacokinetic sample
- 6MWT
- NYHA Functional Class
- Kansas City Cardiomyopathy Questionnaire (KCCQ)

The Physical Exam, 6MWT, NYHA Functional Class, and KCCQ do not need to be performed for patients who are scheduled for a Week 8 visit, due to either up or down titration of study drug.

Following the Final Evaluation (either Week 6 or Week 8), patients will continue to visit the investigational site at weeks 3, 6, 12, 24, 48, and yearly through the Follow-Up Visit (at termination) and/or Termination visit. These visit windows will be based on the date the patient originally enrolled in the TNX-LVO-05 study. Visits that overlap may be combined into one visit.

Patients unable to return at the scheduled Week 6 or 8 visit, may have their final visit extended.

7.2 Weeks 3, 6, 12, 24, 48, and yearly through the Follow-up and/or Termination

visit (Office Visits)

Visits at Weeks 3, 6, 12, 24, 48, and yearly through the Follow-up and/or Termination visit should be performed within ±72 hours of the scheduled weekly visit. These visits may be performed at the investigator's office. For any patients who remain on IV levosimendan, the Follow-Up Visit (at termination) will be calculated as the earlier of two years from the subject's date of entry into the TNX-LVO-05 Study or as soon as possible after study discontinuation, but within 1 week.

During this visit, the following procedures will be performed:

- Vital signs
- Physical Exam
- Hematology and chemistry blood samples
- Body Weight
- 6MWT
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- NYHA Functional Class
- Physician Assessment
- Assess adverse events
- Concomitant medications and/or procedures

If the Week 48 or yearly visit falls within two weeks of any of the IV to oral transition visits (i.e., Week 0, 2, 4, 6 or 8), these visits may be combined.

For subjects who discontinue the study early, the same procedures as listed above should be performed.

Adverse events experienced by the patient since the previous visit, should be assessed at any unscheduled visit at the investigator's office.

7.3 Pharmacokinetic Collection and Analyses

To better understand the plasma levels of levosimendan and its active metabolites, OR-1855 and OR-1896, a pharmacokinetic (PK) blood sample will be drawn at IV to Oral Transition according to the Time and Events Schedule.

Pharmacokinetic samples will be collected for ongoing patients, as of the date of implementation (e.g., IRB approval) of Version 4.1 at investigational sites. Patients who discontinue the study prior to the ability to either consent or physically visit the investigational site will not be required to have a PK sample collected.

7.4 Non-successful transition to oral levosimendan

Patients who do not successfully transition to oral levosimendan may re-start IV levosimendan, within a minimum of 7 days from their last dose of oral levosimendan. Once a patient re-starts IV levosimendan, they will continue to receive study drug based on the original date of entry into the TNX-LVO-05 study (i.e., final visit in the parent study, TNX-LVO-04) return to their weekly IV levosimendan dose regimen they were on prior to starting the oral transition.

Patients that re-start IV levosimendan will not have the opportunity to be given oral levosimendan in the future.

The starting dose of IV levosimendan should be at the same rate the patient was receiving prior to the transition to oral levosimendan. After re-starting IV levosimendan, the patient should be contacted by telephone after 2 weeks to assess for any safety events.

8. STUDY EVALUATIONS AND PROCEDURES

Study procedures will occur according the Time and Events Schedule.

Patients should be instructed to report adverse events associated with their in-home administration of the drug and any concerns that are identified between administration. Each report should be evaluated with respect to the need for an office visit for further assessment of safety.

Any adverse event identified by the patient during unscheduled visits should be recorded and followed, as appropriate, in accordance with Section 7.

8.1.1 Efficacy Measures

6-Minute Walk Test (6MWT)

The 6MWT should be performed at approximately the same time of day at each study visit and ideally, one of the first assessments to be performed.

An online tutorial on how to perform the 6MW test properly will be required of all clinical coordinators who will be performing the test. Only those who successfully complete the tutorial will be allowed to administer the test. In addition, a patient information booklet describing the appropriate effort and performance of the 6MW test will be given to each patient.

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.

- Patient global assessment (based on the KCCQ instrument)
- Physician's Assessment of Functional Class
- Clinical Events: Death and hospitalizations

8.1.2 **Safety Assessments**

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

Any adverse events identified by the patient during unscheduled visits should be recorded and followed, as appropriate, in accordance with Section 7.

Patients should be instructed to report adverse events throughout their participation in the study. Each report should be evaluated with respect to the need for an office visit for further assessment of safety.

8.1.2.1 Medical and Medication History

To be completed at the final office visit in the parent study to ensure subjects meet the inclusion criteria for the study. Any clinically significant history should be noted in the eCRF.

8.1.2.2 Physical Examination (Including Height and Weight)

Abnormalities identified at the final office visit in the parent study 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.

8.1.2.3 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 the subject withdraws from the study, or the discontinuation of the study, whichever occurs first. Serious adverse events will be collected through in the same manner.

8.1.2.4 Vital Signs

Blood pressure should be determined by cuff (using the same method, the same arm, and in the same position throughout the study, as appropriate). 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].

8.1.2.5 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.

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
NT-proBNP

Child-Pugh Class is only required for patients who have documented liver disease.

8.1.3 Electrocardiogram

Subjects have a 12-lead ECG performed as per the Time and Events Schedule. ECGs performed prior to administration of study drug in the parent study (where applicable). Abnormal ECGs may be repeated at the Investigator's discretion.

8.1.3.1 Quality of Life Assessments

The 6-point Likert scale will be replaced with the KCCQ instrument (Attachment 2) and provided to subjects to completed as per the Time and Events Schedule.

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 and are to be recorded on the appropriate AE pages in the eCRF and in source documents. 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 course of 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 as long as 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 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.

Ongoing Adverse Event Collection

During ongoing study and routine standard of care visits, the patient should be asked if they have experienced any of the following changes:

- Palpitations associated with:
    - Shortness of breath
    - Significant lightheadedness
    - Passing out/syncope
- Edema (swelling):

  - Frequency (never, occasionally, constantly)
- Shortness of breath with activity:
  - Frequency (rarely, often, constantly)
- Diuretic use:
  - Changes (increase, no change, decrease)
- Hospitalization or Emergency Room visits

All changes to a patient's health status, including AEs, concomitant medication/procedures, and hospitalizations (including ER visits) must be documented in the case report form.

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 exposure to study drug 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 1 category.

- **Abuse** – Persistent or sporadic intentional intake of 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 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. Medication errors are reportable to the Sponsor as defined below.

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

Medication errors should be collected/reported.

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

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 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 1 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, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE.

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

9.2.4 Serious Adverse Event Collection Timeframe

SAEs must be recorded from the time of signature of Patient Informed Consent through 30 days after completion of the last dose. 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 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.

9.2.6 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).

9.2.7 Regulatory Agency, Institutional Review Board, Independent Ethics Committee, 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.

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 in the 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.

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 9.1 or higher of SAS® (SAS Institute, Cary, NC 27513).

10.4 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.

10.5 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.

10.6 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.

10.7 Prior and Concomitant Medication

Sites must maintain adequate records of concomitant medications and procedures throughout the study. 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.

10.8 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.

10.9 Efficacy Analysis

All efficacy endpoints are considered secondary endpoints. Descriptive statistics for efficacy endpoints will be reported at 3, 6, 12, 24, 48 and Follow-Up Visit (at termination) as well as Week 0 and Week 6 (or 8) for IV to oral transition patients.

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 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Independent Ethics Committees

The Sponsor will provide a summary of the Clinical Study Report within 1 year of the end of the study completion date to the competent authority of the Member State(s) concerned as

required by regulatory requirement(s) and to comply with the Community guideline on GCP (if applicable).

11.1.4 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 commitment 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 CRO and should be handled in accordance with instructions from the Sponsor. Please see the Data Management Plan for further information.

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 reviews 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 within 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.

12. REFERENCES

1. Oktay AA, Rich JD, Shah SJ (2013) The emerging epidemic of heart failure with preserved ejection fraction. Curr Heart Fail Rep 10(4):401–410

2. Oudiz RJ (2007). Pulmonary hypertension associated with leftsided heart disease. Clin Chest Med 28(1):233–241,

3. Hoeper, Marius M., et al. "A global view of pulmonary hypertension." The Lancet Respiratory Medicine 4.4 (2016): 306-322

4. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, et. al. (2009) Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 30(20):2493–2537

5. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, et.al. (2009) ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Associati.Circulation 119(16):2250–2294.

6. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, et.al. (2009) Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 54(1 Suppl):43–54.

7. D. Dixon, A. Trivedi, S. Shah. Combined post- and pre-capillary pulmonary hypertension in heart failure with preserved ejection fraction. 2015. Heart Fail Rev DOI 10.1007/s10741-015-9523-6

8. S. Shaw, D.Kitzman, B. Borlaug, L.van Heerebeek, et al. Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction; A Multiorgan Roadmap. Circulation. 2016;134:73-90. DOI: 0.1161/CIRCULATIONAHA.116.021884

9. Gorter TM, van Veldhuisen DJ, Bauersachs J, Borlaug BA, Celutkiene J, et al. Right heart dysfunction and failure in heart failure with preserved ejection fraction: mechanisms and management. Position statement on behalf of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018 Jan;20(1):16-37. doi: 10.1002/ejhf.1029. Epub 2017 Oct 16. Review.

10. Klapholz M, Maurer M, Lowe AM, Messineo F, Meisner JS, et. al. (2004) Hospitalization for heart failure in the presence of a normal left ventricular ejection fraction: results of the New York Heart Failure Registry. J Am Coll Cardiol 43(8):1432–1438.

11. Haikala H, Kaivola J, Nissinen E, et al. (1995) Cardiac troponin C as a target protein for a novel calcium sensitizing drug, levosimendan. J Mol Cell Cardiol. 27 (9): 1859-66.

12. Haikala H and Linden IB (1995) Mechanisms of action of calcium-sensitizing drugs. J Cardiovasc Pharmacol. 26 Suppl 1: S10-9.

13. Pollesello P, Ovaska M, Kaivola J, et al. (1994) Binding of a new Ca2+ sensitizer, levosimendan, to recombinant human cardiac troponin C. A molecular modelling, fluorescence probe, and proton nuclear magnetic resonance study. J Biol Chem. 269 (46): 28584-90.

14. Sorsa T, Pollesello P and Solaro RJ (2004) The contractile apparatus as a target for drugs against heart failure: interaction of levosimendan, a calcium sensitiser, with cardiac troponin c. Mol Cell Biochem. 266 (1-2): 87-107.

15. Yokoshiki H, Katsube Y, Sunagawa M and Sperelakis N (1997) Levosimendan, a novel Ca2+ sensitizer, activates the glibenclamide-sensitive K+ channel in rat arterial myocytes. Eur J Pharmacol. 333 (2-3): 249-59.

16. Pataricza J, Hohn J, Petri A, et al. (2000) Comparison of the vasorelaxing effect of cromakalim and the new inodilator, levosimendan, in human isolated portal vein. J Pharm Pharmacol. 52 (2): 213-7.

17. Kaheinen P, Pollesello P, Levijoki J and Haikala H (2001) Levosimendan increases diastolic coronary flow in isolated guinea-pig heart by opening ATP-sensitive potassium channels. J Cardiovasc Pharmacol. 37 (4): 367-74.

18. Erdei N, Papp Z, Pollesello P, et al. (2006) The levosimendan metabolite OR-1896 elicits vasodilation by activating the K(ATP) and BK(Ca) channels in rat isolated arterioles. Br J Pharmacol. 148 (5): 696-702.

19. Maytin M and Colucci WS (2005) Cardioprotection: a new paradigm in the management of acute heart failure syndromes. Am J Cardiol. 96 (6A): 26G-31G.

20. Pollesello P and Papp Z (2007) The cardioprotective effects of levosimendan: preclinical and clinical evidence. J Cardiovasc Pharmacol. 50 (3): 257-63.

21. du Toit EF, Genis A, Opie LH, et al. (2008) A role for the RISK pathway and K(ATP) channels in pre- and post-conditioning induced by levosimendan in the isolated guinea pig heart. Br J Pharmacol. 154 (1): 41-50.

22. Louhelainen, M., S. Merasto, P. Finckenberg, E. Vahtola, et. al. Effects of the calcium sensitizer OR-1896, a metabolite of levosimendan, on post-infarct heart failure and cardiac remodelling in diabetic. British Journal of Pharmacology (2010), 160, 142–152.

23. Erdei N, Papp Z, Pollesello P, et al. (2006) The levosimendan metabolite OR-1896 elicits vasodilation by activating the K(ATP) and BK(Ca) channels in rat isolated arterioles. Br J Pharmacol. 148 (5): 696-702.

24. Szilagyi S, Pollesello P, Levijoki J, et al. (2004) The effects of levosimendan and OR-1896 on isolated hearts, myocyte-sized preparations and phosphodiesterase enzymes of the guinea pig. Eur J Pharmacol. 486 (1): 67-74.

25. Banfor PN, Preusser LC, Campbell TJ, et al. (2008) Comparative effects of levosimendan, OR-1896, OR-1855, dobutamine, and milrinone on vascular resistance, indexes of cardiac function, and O2 consumption in dogs. Am J Physiol Heart Circ Physiol. 294 (1): H238-48.

26. Louhelainen M, Merasto S, Finckenberg P, et al. (2009) Effects of calcium sensitizer OR-1986 on a cardiovascular mortality and myocardial remodelling in hypertensive Dahl/Rapp rats. J Physiol Pharmacol. 60 (3): 41-7.

27. Segreti JA, Marsh KC, Polakowski JS and Fryer RM (2008) Evoked changes in cardiovascular function in rats by infusion of levosimendan, OR-1896 [(R)-N-(4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl)acetamid e], OR-1855 [(R)-6-(4-aminophenyl)-5-methyl- 4,5-dihydropyridazin-3(2H)-one], dobutamine, and milrinone: comparative effects on peripheral resistance, cardiac output, dP/dt, pulse rate, and blood pressure. J Pharmacol Exp Ther. 325 (1): 331-40.

28. Kivikko M, Lehtonen L and Colucci WS (2003) Sustained hemodynamic effects of intravenous levosimendan. Circulation. 107 (1): 81-6.

29. Follath F, Cleland JG, Just H, et al. (2002) Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomized double-blind trial. Lancet. 360 (9328): 196-202.

30. Slawsky MT, Colucci WS, Gottlieb SS, et al. (2000) Acute hemodynamic and clinical effects of levosimendan in subjects with severe heart failure. Study Investigators. Circulation. 102 (18): 2222-7.

31. Nieminen MS, Akkila J, Hasenfuss G, et al. (2000) Hemodynamic and neurohumoral effects of continuous infusion of levosimendan in subjects with congestive heart failure. J Am Coll Cardiol. 36 (6): 1903-12.

32. Lilleberg J, Nieminen MS, Akkila J, et al. (1998) Effects of a new calcium sensitizer, levosimendan, on haemodynamics, coronary blood flow and myocardial substrate utilization early after coronary artery bypass grafting. Eur Heart J. 19 (4): 660-8.

33. Ukkonen H, Saraste M, Akkila J, et al. (2000) Myocardial efficiency during levosimendan infusion in congestive heart failure. Clin Pharmacol Ther. 68 (5): 522-31.

34. Packer M, Colucci W, Fisher L, et al. (2013) Effect of Levosimendan on the Short-Term Clinical Course of Patients With Acutely Decompensated Heart Failure. JCHF. 1 (2): 103-11.

35. Mebazaa A, Nieminen MS, Packer M, et al. (2007) Levosimendan vs dobutamine for subjects with acute decompensated heart failure: the SURVIVE Randomized Trial. JAMA. 297 (17): 1883-91.

36. Lilleberg J, Laine M, Palkama T, et al. (2007) Duration of the haemodynamic action of a 24-h infusion of levosimendan in subjects with congestive heart failure. Eur J Heart Fail. 9 (1): 75-82.

37. Kivikko M, Lehtonen L and Colucci WS (2003) Sustained hemodynamic effects of intravenous levosimendan. Circulation. 107 (1): 81-6.

38. Mebazaa A, Nieminen MS, Filippatos GS, et al. (2009) Levosimendan vs. dobutamine: outcomes for acute heart failure subjects on beta-blockers in SURVIVE. Eur J Heart Fail. 11 (3): 304-11.

39. Comín-Colet, J. "Multicenter, double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of intermittent levosimendan in outsubjects with advanced chronic heart failure: the LION Heart Study." Late Breaking Trials II: Heart Failure Management/Heart FAILURE 2015 Congress of the ESC-HFA. 2015.

40. Nieminen, Markku S., et al. "Oral levosimendan in subjects with severe chronic heart failure—the PERSIST study." European journal of heart failure 10.12 (2008): 1246-1254.

41. Hosenpud, Jeffrey D. "Levosimendan, a novel myofilament calcium sensitizer, allows weaning of parenteral inotropic therapy in subjects with severe congestive heart failure." The American journal of cardiology 83.12 (1999): 9-11.

42. Michaels AD, McKeown B, Kostal M, Vakharia KT, Jordan MV, Gerber IL, Foster E, Chaterjee K. Effects of intravenous levosimendan on human coronary vasomotor regulation, left ventricular wall stress, and myocardial oxygen uptake. Circulation 2005;111:1504–9.

43. Grossini E, Caimmi PP, Molinari C, Teodori G, Vacca G. Hemodynamic effect of intracoronary administration of levosimendan in the anesthetized pig. J Cardiovasc Pharmacol 2005;46:333–42.

44. Hasenfuss G, Pieske B, Castell M, Kretschmann B, Maier LS, Just H. Influence of the novel inotropic agent levosimendan on isometric tension and calcium cycling in failing human myocardium. Circulation. 1998;98: 2141–2147

45. De Luca L, Sardella G, Proietti P, Battagliese A, Benedetti G, Di Roma A, Fedel F. Effects of levosimendan on left ventricular diastolic function after primary angioplasty for acute anterior myocardial infarction: a Doppler echocardiographic study. J Am Soc Echocardiogr. 2006 Feb;19(2):172-7.

46. Altenberger J, Parissis JT, Costard-Jaeckle A, et al. Efficacy and safety of the pulsed infusions of levosimendan in outsubjects with advanced heart failure (levorep) study: a multicentre randomized trial. Eur J Heart Fail. 2014;16:898–906.

47. Comin-Colet J, N. Manito, J. Servia-Cubero, J. Delgado, et al. Efficacy and safety of intermittent intravenous outsubject administration of levosimendan in subjects with advanced heart failure: the LION-HEART multicentre randomised trial. European Journal of Heart Failure (2018) doi:10.1002/ejhf.1145.

48. García-González MJ, et al; LAICA Study Investigators. Efficacy and safety of intermittent. Paper presented at: European Society of Cardiology–Heart Failure Association Congress; May 21, AU9 2016; Florence, Italy.

49. Szilagyi S, Pollesello P, Levijoki J, Kaheinen P, Haikala H, Edes I et al. (2004). The effects of levosimendan and OR-1896 on isolated hearts, myocyte-sized preparations and phosphodiesterase enzymes of the guinea pig. Eur J Pharmacol 486: 67–74

50. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: Guidelines for the Six-minute Walk Test. Am J Respir Crit Care Med. 2002;166(1):111-7.

51. Kleber FX, Bollmann T, Borst MM, et al. Repetitive dosing of intravenous levosimendan improves pulmonary hemodynamics in patients with pulmonary hypertension: Results of a pilot study. J Clin Pharmacol. 2009;49:109–15.

52. Hoeper M, Badesch DB, et. al. Definitions and Diagnosis of Pulmonary Hypertension. J Am Coll Cardiol 2013;62: D42–50.

53. Nieminen, Markku S., et al. "Oral levosimendan in patients with severe chronic heart failure—the PERSIST study." European journal of heart failure 10.12 (2008): 1246-1254.

54. Pöder P, Nieminen MS, Airaksinen J, Anttonen O, Harjola V-P, Lilleberg J, et al. Effects of peroral levosimendan in the prevention of further hospitalisations in patients with chronic heart failure. A randomised, double-blind, placebo-controlled, multi-centre, parallel-group study (PERSIST). Clinical study report: Orion Pharma 2006. Report No.: 3001081.

55. Burkhoff, Daniel, et al. "24-hour Levosimendan Infusion Decreases Biventricular Filling Pressures and Increases Cardiac Output at Rest and Exercise in PH-HFpEF." Circulation 142.Suppl_3 (2020): A15294-A15294.

56. Harjola, Veli-Pekka, et al. "Oral levosimendan improves cardiac function and hemodynamics in patients with severe congestive heart failure." The American journal of cardiology 83.12 (1999): 4-8.

57. Jalanko, Mikko, et al. "Oral levosimendan improves filling pressure and systolic function during long-term treatment." Scandinavian Cardiovascular Journal 45.2 (2011): 91-97.

13. APPENDICES

13.1 APPENDIX 1: Summary of Changes for Previous Protocol Amendments

Revisions included in Amendment 2 to the protocol, Version 4.1, dated 02 February 2021.

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: ~~3.0, 19 June 2019,~~ 4.1, 25 January 2021
Global Change		Revised Stuart Rich, MD's title to Chief Medical Officer, Tenax Therapeutics, Inc.
Global Change		Ongoing patients will be transitioned from weekly IV levosimendan administration to daily oral levosimendan administration up to 3 mg, as tolerated, for the remainder of the study. Patients will continue receiving levosimendan in this Open-Label Extension Study, TNX-LVO-05, ~~for up to 2 years.~~ and continue for 3 years following transition to oral levosimendan or termination of the trial by the patient or physician decision.
Global Change		Study visits that occur after Week 48 will occur yearly.
Global Change		Replaced the Likert Scale with the KCCQ instrument for patient QOL assessment.
Time and Events Schedule		Updated to reflect the addition of the 6-week transition period for patients transitioning from IV to oral levosimendan. Footnotes have been updated commensurate to changes.
18	BACKGROUND INFORMATION	Section 1.1 explains the rationale for transitioning patients from IV to Oral levosimendan.
20	BACKGROUND INFORMATION	Section 1.3 provides details of oral levosimendan use from the PERSIST study

20	BACKGROUND INFORMATION	Section 1.3.4 includes information from the PERSIST study, of patients who were randomised to either oral levosimenan or placebo in patients with severe CHF.
22	BACKGROUND INFORMATION	Section 1.3.5 includes data from the completed TNX-LVO-04 (”HELP”) study.
23	BACKGROUND INFORMATION	Section 1.3.6: Additional safety information included for the 8 studies of oral levosimendan in HF patients, as well as safety data from the HELP study.
24	BACKGROUND INFORMATION	Section 1.3.7: Rationale for Chronic ~~Intermittent (weekly)~~ Oral Levosimendan ~~for PH-HFpEF Patients~~ Updated the third and fourth bullet in this section to remove reference to IV and change to oral levosimendan
26	BACKGROUND INFORMATION	Section 1.3.8: Target Plasma Concentrations of OR-1896 in ~~intermittent~~ chronic treatment of PH-HFpEF Patients Included figure for comparison of plasma concentrations between the HELP and PERSIST studies.
31	STUDY OBJECTIVES AND PURPOSE	Section 2.3.1: (new section) Regimen Transition: Weekly Intravenous to Daily Oral Levosimendan
31	STUDY OBJECTIVES AND PURPOSE	Section 2.5: Updated to include details of procedural steps to be taken as patients transition from IV to oral levosimendan
35	PRIOR AND CONCOMITANT TREATEMENT	Section 4.3: redefined the allocation of treatement of subjects from IV to oral levosimendan
36	INVESTIGATIONAL PRODUCT	Section 5: Included background information for oral levosimendan, inclucing Packaging, Labeling, and dosing
38	STUDY PROCEDURES	Section 6: Included instructions on procedures that are to be followed for transition of patients from IV to oral levosimendan. Section 6.2 added. Included language pertaining to ongoing collection of adverse events.
42	STUDY PROCEDURES	Section 6.4: Added the requirement for PK blood draws at Week 0, 4, and 6 (or 8) for patients transitioning to oral levosimendan.

49	Study-Specific Events of Interest	Section 8.1.5: Included ”Ongoing Adverse Event Collection”
80	ATTACHMENT 2	Kansas City Cardiomyopathy Questionnaire (KCCQ) added
85	ATTACHMENT 4	Added a patient diary to record daily BP, HR, and study drug consumption

Revisions included in Amendment 2 to the protocol, Version 3.0, dated 19 June 2019.

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, 31 October 2018~~Version 3.0, 19 June 2019
Global Change		Clarified that the Follow-Up Visit and the Termination Visit should be the same visit. The last office visit and study assessments in TNX-LVO-05, will be the "Follow-up Visit (at termination)" at the completion of the 2 year study, within 1 week of the last dose.
12	SYNOPSIS: Diagnosis and main criteria for inclusion and exclusion: Inclusion Criteria:	(modified to be consistent with the specific inclusion criterion in body of the protocol, Section 3.1) 2. ~~Received levosimendan as treatment for~~ Completed double-blind therapy in a PH-HFpEF in a clinical study sponsored by Tenax Therapeutics, Inc.
		(inclusion criterion corrected to be consistent with the specific inclusion criterion in body of the protocol, Section 3.1. This change maintains the criterion for female contraception as identified in the parent study, TNX-LVO-04, and corrects the reference to "male" contraception. Reproductive toxicology studies have not identified a need for male contraception in the use of levosimendan.) 4. ~~Male patients and f~~Female patients of childbearing potential must agree to use a highly effective method of contraception.

12	SYNOPSIS: Diagnosis and main criteria for inclusion and exclusion: Exclusion Criteria:	(added to be consistent with the exclusion criteria in body of the protocol, Section 3.2; these exclusions were inadvertently not included in the list of criteria within the Synopsis.). 4. Inability to comply with planned study procedures 5. Patients with scheduled lung or heart transplant or cardiac surgery 6. Dialysis developed since enrollment in parent study (either hemodialysis, peritoneal dialysis, continuous venovenous hemofiltration, or ultrafiltration) 7. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m2 8. Liver dysfunction with Child Pugh Class B or C (see Attachment 2) 9. Evidence of systemic bacterial, systemic fungal, or viral infection refractory to treatment 10. Weight > 150kg 11. Systolic blood pressure (SBP) cannot be managed to ensure SBP >100 mmHg at initiation of study drug 12. Heart rate >100 bpm with study drug, persistent for at least 10 minutes at screening. 13. Hemoglobin < 80 g/L 14. Serum potassium < 3.0 mmol/L or > 5.5 mmol/L that is unresponsive to correction
13	SYNOPSIS Duration of treatment:	(corrected typographical error) Patients will continue receiving levosimendan in this Open-Label Extension Study, TNX-LVO-045, for up to 2 years.
15	TIME AND EVENTS SCHEDULE	(added row for PICC line to Port-a-Cath conversion specified in Section 5.4.1)
16	Footnotes for Time and Events Schedule	(added footnote regarding PICC line to Port-a-Cath conversion) 7. If at the Week 3 visit the open-label levosimendan has been well-tolerated by the patient, the investigator should review with the subject the opportunity to convert the PICC line to a port-a-cath in the coming weeks (Section 5.4.1).

24	2.3 Study Design	(paragraph removed for clarity; tudy length and office visits are identified in the following paragraph;the home health care nurse assessments at Week 1 and 2 provide information to the site regarding patient health status.) ~~Clinic visits for safety assessments and study drug dispensing will be performed at Week 3, week 6, and then every 12 weeks (± 14 days) through 48 weeks study , or until treatment discontinuation criteria are met. Patients will be contacted at Weeks 1 and 2 after beginning the trial to assess health status.~~
25	3. STUDY POPULATION 3.1 Inclusion Criteria Enrollment Criteria:	(added to be consistent with the inclusion criterion in the Synopsis section of the protocol) 3. <u>May, in the opinion of the Investigator, benefit from continued levosimendan treatment.</u>
25	3.2 Exclusion Criteria	(revised to be consistent with the text for this exclusion in the Synopsis section of the protocol) 15. Discontinued treatment ~~of blinded drug~~ <u>in the parent study</u> for any reason other than study completion or Sponsor termination of the study.
26	3. STUDY POPULATION 3.2 Exclusion Criteria	(revised to exclude subjects only if a transplant or cardiac surgery is scheduled) 5. Patients <u>with scheduled</u> ~~planning~~ lung or heart transplant or cardiac surgery ~~in the next 4 months~~
		(revised to exclude only those subjects refractory to treatment of infections) 9. Evidence of systemic bacterial, systemic fungal, or viral infection ~~in last 2 weeks~~ <u>refractory to treatment</u>
		(revised to be consistent with the latest version in the parent study, TNX-LVO-04, Version 4.0, dated 15 May 2019, which expanded the weight range to include those patients between 135 and 150 kg that can be effectively managed on the cath lab table) 10. Weight > ~~135~~ <u>150</u>kg
		(revised to specify exclusion only of those subjects that are unresponsive to management of serum potassium)

		14. Serum potassium < 3.0 mmol/L or > 5.5 mmol/L at baseline that is unresponsive to management
28	5. INVESTIGATIONAL PRODUCT 5.1 Levosimendan	(corrected recipient of levosimendan supplies in this open-label extension study) Levosimendan will be provided to ~~investigators~~ the subjects by the sponsor as a sterile clear, yellow to orange solution in clear glass vials.
30	5.4.1 Dosage and Administration	(corrected reference to time of dose escalation) Patients may have a dose escalation at Weeks 3 ~~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 4) or other prohibitive rationale.
		(clarified instructions regarding transition from PICC line to port-a-cath in patients choosing to continue PICC lines after Week 3) A subject that chooses to continue with a PICC line after Week 3 will be transitioned to a port-a-cath once the PICC line fails or will be discontinued from the study.
		(corrected incorrect reference to preoperative subjects) 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.
31	5.4.2 Self-Administration of Levosimendan	(clarified statement; removed extraneous phrase) The subject will be instructed on the preparation, administration, and disposal/return of levosimendan (including ancillary supplies) ~~will be provided to each subject~~ by the home healthcare nurse.
33	5.8 Drug Accoutability	(clarified to remove reference to site, as drug is shipped to subject's home) 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.
		(clarified to remove reference to sudy blind, as this is an open-label study.) 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.~~
		(clarified to remove reference to site, as drug is shipped to subject's home) Based on entries in the ~~site~~ drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned.

33	5.9 Subject Compliance	(clarified that the eCRF will document details of each administration that is supported by the home health care nurse; removed reference to study drug dipensed at the site) The details of each administration supported by a home health care nurse will be recorded in the eCRF. ~~The investigator or designated study personnel will maintain a log of all study drug dispensed and returned~~.
36	6.4 Weeks 3, 6, 12, 24, Follow-Up Visit (at termination) (Office Visits)	(added NYHA Functional Asssessment to the list of patient assessments at each office visit in keeping with the Time and Events Schedule in the Synopsis) • NYHA Functional Class
37	6.5.2 Safety Assessments	(modified leading section of safety assessments to emphasize the subject's role in identifying and communicating safety information to the clinical site; site role in evaluation and subject follow-up) Any adverse events identified by the patient during unscheduled visits should be recorded and followed, as appropriate, in accordance with Section 7. Patients should be instructed to report adverse events associated with their in-home administration of the drug and adverse events of concern that are identified between administration. Each report should be evaluated with respect to the need for an office visit for further assessment of safety.
45	7.2.4 Serious Adverse Event Collection Timeframe	(sentence added to identify full time window for recording of SAEs) SAEs must be recorded from the time of signature of Patient Informed Consent through 30 days after completion of the last infusion.
47	8.2 Clinical Data Management	(clarified sentence; corrected typographical omission) Data collected in the 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.
60	Appendix 1 Summary of Changes for Previous Protocol Amendments	(added this table of revisions included in TNX-LVO-05, Version 3.0)

Revisions included in Amendment 1 to the protocol, dated 31 October 2018 (Version 2.0)

1. Removed right heart catheter and hemodynamic measurements at Week 48
2. Removed echocardiography at Week 48
3. The study will end at 2 years

14. ATTACHMENTS

14.1 ATTACHMENT 1: 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 into 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.

14.2 ATTACHMENT 2: Kansas City Cardiomyopathy Questionnaire

The Kansas City Cardiomyopathy Questionnaire

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. Heart failure affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by heart failure (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an **X** in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	❑	❑	❑	❑	❑	❑
Showering/Bathing	❑	❑	❑	❑	❑	❑
Walking 1 block on level ground	❑	❑	❑	❑	❑	❑
Doing yardwork, housework or carrying groceries	❑	❑	❑	❑	❑	❑
Climbing a flight of stairs without stopping	❑	❑	❑	❑	❑	❑
Hurrying or jogging (as if to catch a bus)	❑	❑	❑	❑	❑	❑

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (shortness of breath, fatigue or ankle swelling) changed? My symptoms of **heart failure** have become …

	Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over

1. Heart failure affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by heart failure (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

					the last 2 weeks
❑	❑	❑	❑	❑	❑

3. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1–2 times a week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you? It has been …

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bother some	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
❑	❑	❑	❑	❑	❑

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1–2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑	❑	❑

6. Over the past 2 weeks, how much has your **fatigue** bothered you? It has been …

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bother some	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
❑	❑	❑	❑	❑	❑

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1–2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑	❑	❑

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you? It has been …

1. Heart failure affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by heart failure (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bother some	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
❑	❑	❑	❑	❑	❑

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every day	1–2 times a week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** sure	**Completely** sure
❑	❑	❑	❑	❑

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse? (for example, weighing yourself, eating a low salt diet, etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
❑	❑	❑	❑	❑

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
❑	❑	❑	❑	❑

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
❑	❑	❑	❑	❑

1. Heart failure affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by heart failure (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I felt that way **all of the time**	I felt that way **most of the time**	I **occasionally** felt that way	I **rarely** felt that way	I **never** felt that way
❑	❑	❑	❑	❑

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Please place an **X** in one box on each line

Activity	**Severely** limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	❑	❑	❑	❑	❑	❑
Working or doing household chores	❑	❑	❑	❑	❑	❑
Visiting family or friends out of your home	❑	❑	❑	❑	❑	❑
Intimate relationships with loved ones	❑	❑	❑	❑	❑	❑

14.3 ATTACHMENT 3: Cardiac Event Recommendations and Management

Changes in BP or HR that could represent a significant safety concern should be reported to the treating physician.

If the subject meets any of the dose-limiting event criteria, the following actions on study drug should be undertaken:

1. Blood pressure (systolic) management
    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 **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 dose
3. **Symptomatic** low BP management
    a. Follow recommendations of asymptomatic scenario (above), **and**
        i. BP <100 mild symptoms = levosimendan dose reduction
        ii. BP <100 severe symptoms = IV phenylephrine and levosimendan dose reduction
        iii. BP <90 on lowest dose = discontinue study
4. Sinus tachycardia at rest
    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 dose reduction
    d. HR >120 (validated) without symptoms = obtain ECG do determine if sinus tachycardia or atrial-fibrillation. *(If HR>120, the treating physician should be contacted.)*
        i. If sinus tachycardia = levosimendan dose reduction or withdraw
        ii. If atrial fibrillation = heart rate drug management
    e. Persistent HR>120 despite any/all above measures = discontinue study

14.4 ATTACHMENT 4: Study Drug Dose and Dosing Table

Preparation of the infusion

Levosimendan 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 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 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 0.1 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 0.1 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.

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 infusion.

Patient's weight (kg)	Infusion rate (mL/h)		
	0.1 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.

14.5 ATTACHMENT 5: Patient Diary of Daily Heart Rate and Blood Pressure Readings

Week 0 through Week 2: *(#)* ____ capsules per day *(#, as directed by physician)*

Each morning, please monitor your blood pressure and heart rate. You should be sitting down and at rest **for at least five minutes** before taking your blood pressure and heart rate. The numbers you write down should be the same as those that appear on the monitor screen (do not round the numbers up or down). In the comments section, please write down anything that could have affected your reading, such as feeling unwell or changes in your medication.

NOTE: If your heart rate above 110 or your Systolic Blood Pressure is below 100, please call your doctor.

Date	*Time*	*Heart Rate*	*Systolic BP (top number)*	*Diastolic BP (bottom number)*	*Study Drug # of capsules taken daily*	*PLEASE CHECK IF YOU ARE EXPERIENCING ANY OF THE FOLLOWING:*
						☐ Palpitations ☐ Light headedness ☐ Chest pain ☐ Worsening shortness of breath ☐ Worsening edema (swelling) ☐ Other_____
						☐ Palpitations ☐ Light headedness ☐ Chest pain ☐ Worsening shortness of breath ☐ Worsening edema (swelling) ☐ Other_____

Week 2 through Week 4: *(#)* ____ capsules per day *(#, as directed by physician)*

Each morning, please monitor your blood pressure and heart rate. You should be sitting down and at rest **for at least five minutes** before taking your blood pressure and heart rate. The numbers you write down should be the same as those that appear on the monitor screen (do not round the numbers up or down). In the comments section, please write down anything that could have affected your reading, such as feeling unwell or changes in your medication.

NOTE: If your heart rate above 110 or your Systolic Blood Pressure is below 100, please call your doctor.

Date	*Time*	*Heart Rate*	*Systolic BP (top number)*	*Diastolic BP (bottom number)*	*Study Drug # of capsules taken daily*	*PLEASE CHECK IF YOU ARE EXPERIENCING ANY OF THE FOLLOWING:*
						☐ Palpitations ☐ Light headedness ☐ Chest pain ☐ Worsening shortness of breath ☐ Worsening edema (swelling) ☐ Other_____
						☐ Palpitations ☐ Light headedness ☐ Chest pain ☐ Worsening shortness of breath ☐ Worsening edema (swelling) ☐ Other_____

Week 4 through Week 6: *(#) ____* capsules per day *(#, as directed by physician)*

Each morning, please monitor your blood pressure and heart rate. You should be sitting down and at rest **for at least five minutes** before taking your blood pressure and heart rate. The numbers you write down should be the same as those that appear on the monitor screen (do not round the numbers up or down). In the comments section, please write down anything that could have affected your reading, such as feeling unwell or changes in your medication.

NOTE: If your heart rate above 110 or your Systolic Blood Pressure is below 100, please call your doctor.

Date	*Time*	*Heart Rate*	*Systolic BP (top number)*	*Diastolic BP (bottom number)*	*Study Drug # of capsules taken daily*	*PLEASE CHECK IF YOU ARE EXPERIENCING ANY OF THE FOLLOWING:*
						☐ Palpitations ☐ Light headedness ☐ Chest pain ☐ Worsening shortness of breath ☐ Worsening edema (swelling) ☐ Other_____
						☐ Palpitations ☐ Light headedness ☐ Chest pain ☐ Worsening shortness of breath ☐ Worsening edema (swelling) ☐ Other_____

Week 6 through Week 8: *(#)* ____ capsules per day *(#, as directed by physician)*

Each morning, please monitor your blood pressure and heart rate. You should be sitting down and at rest **for at least five minutes** before taking your blood pressure and heart rate. The numbers you write down should be the same as those that appear on the monitor screen (do not round the numbers up or down). In the comments section, please write down anything that could have affected your reading, such as feeling unwell or changes in your medication.

NOTE: If your heart rate above 110 or your Systolic Blood Pressure is below 100, please call your doctor.

Date	*Time*	*Heart Rate*	*Systolic BP (top number)*	*Diastolic BP (bottom number)*	*Study Drug # of capsules taken daily*	*PLEASE CHECK IF YOU ARE EXPERIENCING ANY OF THE FOLLOWING:*
						☐ Palpitations ☐ Light headedness ☐ Chest pain ☐ Worsening shortness of breath ☐ Worsening edema (swelling) ☐ Other_____
						☐ Palpitations ☐ Light headedness ☐ Chest pain ☐ Worsening shortness of breath ☐ Worsening edema (swelling) ☐ Other_____