A Phase 2 Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Effects of Multiple Subcutaneous Injections of Elamipretide on Left Ventricular Function in Subjects with Stable Heart Failure with Reduced Ejection Fraction

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21st March 2017

CLINICAL STUDY PROTOCOL

A Phase 2 Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Effects of Multiple Subcutaneous Injections of Elamipretide on Left Ventricular Function in Subjects with Stable Heart Failure with Reduced Ejection Fraction

Study Phase:	Phase 2
Study Number:	SPIHF-201
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Sponsor:	Stealth BioTherapeutics Inc. 275 Grove Street, Suite 3-107 Newton, MA 02466 Unites States of America
Sponsor Clinical Lead:	James Carr, PharmD

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PROTOCOL APPROVAL

Protocol Title:	A Phase 2 Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Effects of Multiple Subcutaneous Injections of Elamipretide on Left Ventricular Function in Subjects with Stable Heart Failure with Reduced Ejection Fraction
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James Carr, PharmD Date

Vice President, Clinical Development

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for elamipretide (MTP-131). I have read the SPIHF-201 protocol and agree to conduct the study as outlined. I confirm that I will conduct the study in accordance with ICH GCP guidelines. I will also ensure that sub-Investigator(s) and other relevant members of my staff have access to copies of this protocol, and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date (DD/MMM/YYYY)

1. SYNOPSIS

Name of Sponsor/Company: Stealth BioTherapeutics Inc.

Investigational Product: Elamipretide (MTP-131)

Title of Study: A Phase 2 Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Effects of Multiple Subcutaneous Injections of Elamipretide on Left Ventricular Function in Subjects with Stable Heart Failure with Reduced Ejection Fraction

Study Center(s): This study will be conducted in up to 20 centers in Europe

Objectives:

Primary:

To evaluate the effects of multiple subcutaneous (SC) doses of elamipretide on left ventricular end systolic volume (LV ESV) assessed by cardiac Magnetic Resonance Imaging (MRI)

Secondary:

- To evaluate the safety and tolerability of multiple SC doses of elamipretide
- To evaluate the effects of multiple SC doses of elamipretide on LV systolic and diastolic function, LV volumes, LV global longitudinal strain, left atrial (LA) volume, LV mass, mitral and tricuspid regurgitation severity, and right ventricular (RV) function.

Exploratory:

To evaluate the effects of multiple SC doses of elamipretide on:

- 6-minute walking distance
- Quality of Life
- N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels

Methodology:

This is a randomized, double-blinded, placebo-controlled, multiple dose study in subjects with stable heart failure with reduced ejection fraction (HFrEF). After completing the screening period, approximately 70 subjects will be randomized, in a 1:1:1 ratio, to receive either placebo, 4 mg elamipretide, or 40 mg elamipretide once daily for 28 consecutive days.

Each treatment group will go through 3 distinct periods: Screening, Treatment and Follow-up. Study procedures, their timing, and additional details for the three study periods are found in the Study Schedule in Attachment 1 and are detailed in the protocol. Details regarding the clinical laboratory tests to be performed are found in Attachment 2 and are detailed in the protocol.

Number of Subjects: Around 70 subjects will be randomized

Inclusion Criteria:

A subject must meet all of the following criteria prior to Day 1 to be eligible for inclusion in the study:

1. Willing and able to provide signed informed consent form (ICF) prior to participation in any study-related procedures.
2. Age ≥40 and ≤80 years.
3. A known history of chronic ischemic or non-ischemic cardiomyopathy of at least 6 months duration from the time of the initial diagnosis or signs and symptoms consistent with heart failure.
4. Receiving heart failure (HF) treatment, including, but not limited to, angiotensin converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB), and an evidence-based beta blocker for the treatment of HF. Subjects who cannot tolerate ACEI or ARB due to reduced renal function or hypotension are eligible. Subjects may be receiving aldosterone antagonists, but this is not a requirement for the study.
5. HF is considered to be stable in the judgment of the Investigator AND doses of HF treatment have been stable for at least 1 month prior to the Screening Visit.
6. In normal sinus rhythm (electrocardiogram documented) at Screening and Day 1 and no history of atrial fibrillation in the past 12 months
7. No hospitalization related to HF within 1 month prior to the Screening Visit.
8. Left Ventricular Ejection Fraction (LVEF) ≤ 40% by 2-D echocardiography at Screening.
9. At least 3 viable segments (hyperenhancement ≤ 25%) by a qualifying delayed gadolinium-enhanced cardiac MRI examination at Screening (confirmed by independent core lab).
10. Willing to adhere to the study requirements for the length of the trial.
11. Women of childbearing potential must agree to use 1 of the following methods of birth control from the date they sign the ICF until two months after the last dose of study medication:
    a. Abstinence, when it is in line with the preferred and usual lifestyle of the subject. Subject agrees to use an acceptable method of contraception should they become sexually active.
    b. Maintenance of monogamous relationship with a male partner who has been surgically sterilized by vasectomy (the vasectomy procedure must have been conducted at least 60 days prior to the Screening Visit or confirmed via sperm analysis).
    c. Barrier method (e.g., condom or occlusive cap) with spermicidal foam/gel/film/cream AND either hormonal contraception (oral, implanted, or injectable) or an intrauterine device or system.

Note: Non-childbearing potential is defined as surgical sterilization (e.g., bilateral oophorectomy, hysterectomy, or tubal ligation) or postmenopausal (defined as permanent cessation of menstruation for at least 12 consecutive months prior to the Screening Visit).

Exclusion Criteria:

A subject who meets any of the following criteria at Screening will be excluded from the study:

1. History of any concurrent medical condition which, in the opinion of the Investigator, significantly increases the potential risks associated with administration of study medication or any other aspect of study participation.
2. Any contraindication to MRI scanning as assessed by local MRI safety questionnaire, which may include:
    a. History of intra-orbital metal fragments which have not been removed
    b. Severe claustrophobia
    c. Non-MRI safe cochlear implant(s) or intracranial aneurysm clips
    d. Extensive tattoos located on the torso that contain metallic inks
    e. Other non-removable implanted metallic or electronic devices that have not been determined to be MRI safe
    f. Inability to lie flat
3. Inadequate echocardiogram image quality (defined as poor sound transmission and/or < 10 endocardial segments seen).
4. LVEDD indexed to Body Surface Area is > 45 mm/m^2 assessed by 2-D echocardiography.
5. Coronary or peripheral revascularization procedures, valvular procedures, OR any major surgical procedure within 3 months prior to the Screening Visit.
6. Acute coronary syndrome, stroke or transient ischemic attack (TIA) within 3 months prior to the Screening Visit.
7. Obstructive or restrictive cardiomyopathy, infiltrative diseases of the myocardium (e.g., amyloid, sarcoid, etc.) myocarditis, or reductions in LV function thought to be secondary primarily to valvular heart disease, prior cardiac valve surgery or known aortic stenosis.
8. The presence or anticipated placement of any pacemaker, implantable cardioverter defibrillator (ICD), or cardiac resynchronization therapy (CRT) devices during the ensuing 6-week study period.
9. Presence of second degree or advanced heart block.

10. Uncontrolled hypertension defined as a systolic blood pressure > 160 mmHg or a diastolic blood pressure > 110 mmHg on at least two consecutive readings.
11. Presence of any left ventricular thrombus, pericardial disease, uncorrected thyroid disease or a dyskinetic left ventricular aneurysm.
12. History of cancer that causes symptoms, disabilities, or is likely to lead to hospitalization or treatment in the next 12 months.
13. Currently receiving treatment with chemotherapeutic agents or immunosuppressant agents or has received prior radiation therapy to the chest.
14. Liver enzymes (alanine aminotransferase [ALT] AND/OR aspartate aminotransferase [AST]) elevation > 3 times the upper limit of normal (ULN).
15. Total bilirubin > 1.5 times ULN in the absence of Gilbert's Syndrome.
16. Bleeding diathesis or any known blood dyscrasia.
17. Anemia, defined as hemoglobin < 9 g/dL or planned blood transfusions in the next 6 weeks.
18. Estimated glomerular filtration rate (eGFR) < 30 mL/min, using the Modification of Diet in Renal Disease (MDRD) Study equation:

    eGFR (mL/min/1.73 m2) = 175 x $(Scr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American)
19. History of hepatitis B, hepatitis C or Human Immunodeficiency Virus (HIV) infection, or diagnosis of immunodeficiency.
20. Known active drug or alcohol abuse within 1 year of the Screening Visit. Alcohol abuse is defined as 15 or more drinks for men per week or 8 or more for women.
21. Recipient of any investigational drugs, stem cell or gene therapies, or devices OR participation in another clinical trial, within 3 months prior to the Screening Visit.
22. Any significant acute or chronic medical or psychiatric illness that, in the judgment of the Investigator, could compromise the subject's safety, limit subject's ability to complete the study, and/or compromise the objectives of the study.
23. Female subjects who are pregnant, planning to become pregnant, or lactating.
24. Currently requiring any changes in doses of cardiovascular medication (including diuretics) in order to control worsening of HF symptoms.
25. Known allergy to gadolinium.
26. Currently receiving treatment with therapeutic doses of anticoagulants. Antiplatelet therapy used to prevent cardiovascular disease (primary prevention) or to treat chronic disease (secondary prevention) is permitted, as well as vitamin K antagonists.
27. Currently receiving treatment with sacubitril/valsartan or trimetazidine.

Investigational product, dosage and mode of administration: Elamipretide (MTP-131) will be supplied as 40 mg/1 mL of sterile solution for subcutaneous injection. The doses of elamipretide will be 4 mg or 40 mg administered as a once daily SC injection.

Planned Study Duration:

Screening Period: Up to 28 days

Treatment Period: At least 28 days

Follow-up Period: 14 days

Reference therapy, dosage and mode of administration: The placebo for this trial will be composed of the excipients used to manufacture the investigational drug but without the active drug substance. The placebo will be handled and administered identically as active drug.

Criteria for evaluation:

Primary Endpoints

Change from baseline in left ventricular end systolic volume (LV ESV) assessed by cardiac MRI

Secondary Endpoints

- Adverse events (AEs)
- Changes from baseline in vital signs
- Changes from baseline in electrocardiograms (ECGs)
- Changes from baseline in clinical laboratory evaluations
- Changes from baseline in the following parameters assessed by cardiac MRI:
    - LV EF
    - LV end diastolic volume (EDV)
- Changes from baseline in the following parameters assessed by echocardiography:
    - E/A (ratio between early and late mitral inflow velocity),
    - E/e' (Ratio between early mitral inflow velocity and mitral annular early diastolic velocity)
    - LV EDV, LV ESV and biplane EF
    - LV global longitudinal strain
    - LA volume
    - LV mass
    - Mitral regurgitation severity
    - Tricuspid regurgitation severity

- RV fractional area change
- RV systolic pressure (RVSP)

Exploratory Endpoints

- Changes from baseline in:
  - Distance walked (meters) on the 6-minute walk test (6MWT)
  - Kansas City Cardiomyopathy Questionnaire (KCCQ) score
  - Levels of N-terminal pro-brain natriuretic peptide (NT-pro-BNP)
  - Change in Borg dyspnea scale

Statistical methods:

Data will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minima and maxima) for continuous variables and using frequencies and percentages for discrete variables. Data will be presented by treatment group, as appropriate. Each active dose will be tested against placebo.

For primary and secondary efficacy endpoints, the change from baseline in all continuous endpoints will be summarized using descriptive statistics (mean, median, standard deviation, minimum, maximum) by treatment group. Additional analyses will be performed according to the Statistical Analysis Plan (SAP).

Safety data analysis will be conducted on all subjects in the Safety Population. The number and percentage of subjects experiencing one or more treatment emergent AEs will be summarized by treatment group, relationship to study medication, and severity. Listings of subjects who experience withdrawal due to an AE, serious AEs, suspected unexpected serious adverse reactions, and/or death will be presented. Laboratory parameters will be summarized using descriptive statistics, by post-dosing shifts relative to baseline where appropriate, and data listings of clinically significant abnormalities. Vital signs and ECG data will be summarized by changes from baseline values using descriptive statistics.

Sample Size:

The initial sample size of 45 patients was based on the assumption that a sample size of 15 subjects per treatment group provided 90% power to detect an 8 milliliter (mL) difference between treatment groups in LV ESV, as measured by MRI, assuming a standard deviation of 6.5 mL.

A revised estimate of the standard deviation, based on a review of blinded LV ESV data from the first 11 subjects who completed treatment, suggests it may ultimately be as high as 9.4 mL. Accordingly, the sample size is being increased to around 22 subjects per treatment group, which provides 80% power to detect the aforementioned 8 mL difference between treatment groups. If necessary, the standard deviation will be reassessed in blinded fashion and the sample size modified accordingly.

2. TABLE OF CONTENTS

3. ABBREVIATIONS AND DEFINITIONS

Term	Definition
6MWT	Six-minute walk test
ACEI	Angiotensin converting enzyme inhibitors
AE	Adverse event
ALT	Alanine aminotransferase
ARB	Angiotensin receptor blockers
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration versus time curve
$AUC_{0-\tau}$	Area under the plasma concentration vs time curve from time 0 to end of the dosing interval
BMI	Body mass index
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum plasma concentration
CRT	Cardiac resynchronization therapy
E/A	Ratio between early and late mitral inflow velocity
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic data capture
EDV	end-diastolic volume
E/e’	Ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e’)
EF	ejection fraction
eGFR	estimated glomerular filtration rate
ESV	end-systolic volume
GCP	Good Clinical Practice
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HIV	Human Immunodeficiency Virus
IB	Investigator’s Brochure
ICD	implantable cardioverter defibrillator
ICF	informed consent form

Term	Definition
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	investigational medicinal product
IRB	Institutional Review Board
ISR	Injection Site Reaction
IV	intravenous
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	left atrial
LV	left ventricular
LVEDD	left ventricular end-diastolic dimension
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
MRI	magnetic resonance imaging
MTP-131	elamipretide or Bendavia™
NT-pro-BNP	N-terminal pro-brain natriuretic peptide
PK	pharmacokinetic(s)
PT	preferred term
RV	right ventricular
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

4. INTRODUCTION

This study will be conducted in strict accordance with the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, ICH GCP guideline, and all applicable laws and regulations. For detailed information on the study medication and the nonclinical and clinical studies conducted to date, please refer to the most recent edition of the MTP-131 Investigator's Brochure (IB).

4.1. Heart Failure

It is estimated that approximately 1-2% of the adult population in developed countries has Heart Failure (HF) and the prevalence is rising to ≥ 10% among persons 70 years of age or older (1). HF incidence is continuously increasing. The overall worldwide economic cost of HF in 2012 was estimated at 108 billion US dollars per annum (2).

Chronic systolic HF is a multisystem disease. Although initiated by a reduction in cardiac function, chronic HF is characterized by systemic responses induced by declines in cardiac function, particularly regarding neurohormonal activation (renin-angiotensin-aldosterone system and the sympathetic nervous system). Besides the negative effect on the myocardium, these systemic responses negatively impact the blood vessels, kidneys, muscles, bone marrow, lungs and liver (3, 4). Exercise intolerance is widely recognized as a defining symptom in individuals with chronic HF, limiting physical activity and impairing quality of life. This attenuated exercise capacity has been traditionally attributed to the "central" limitations associated with a malfunctioning cardiac pump. In addition, many non-cardiac factors may contribute substantially to exercise intolerance: changes in peripheral vascular function, skeletal muscle physiology, pulmonary gas exchange, neurohormonal and reflex autonomic activity, and renal sodium handling (5).

Despite the significant improvement in symptoms and survival observed with pharmacologic blockade of the renin-angiotensin and beta adrenergic systems, such drug therapy generally has had limited impact on exercise capacity.

This has led to the concept that multi-targeted mechanistic approaches to HF are required to successfully translate experimental interventions into protection against the clinical manifestations of the disease state, as well as beneficially impact its associated major adverse events, including recurrent hospitalization and death. Such a broad-based approach must include therapies that simultaneously impact multiple affected organ systems and cellular mechanisms including the:

- Heart: Limited cardiac output
- Mitochondria: Limited energetics
- Skeletal Muscle: Limited bulk and strength
- Endothelium: Limited vascular function
- Lungs: Limited gas exchange
- Kidneys: Abnormal salt and volume regulation

Elamipretide, with its multi-organ beneficial actions on function and metabolism *in vitro* and in animal models, is a promising candidate for targeting the complex interplay of factors that ultimately result in the syndrome of clinical HF. The potential of elamipretide to treat the multiple organs systems and organelles that contribute to the HF state represents an important opportunity to address a critical and unmet clinical need.

4.2. Elamipretide Risk/Benefit Assessment

4.2.1. Potential Benefits

In animal models of HF, elamipretide has been shown to beneficially impact the major potential therapeutic targets for HF. In canine studies of severe well established HF both a single infusion and 3 months of daily elamipretide injections improved left ventricular (LV) ejection fraction, LV end diastolic pressure, and rate of rise of LV pressure (dP/dt_{max}), without changes in heart rate or mean aortic pressure. In different murine models of heart failure, elamipretide ameliorated cardiac hypertrophy and enlargement, systolic and diastolic dysfunction, and myocardial fibrosis.

In a Phase 1 trial (SPIHF-101) evaluating single ascending IV doses of elamipretide in 24 patients with moderate chronic HF receiving concomitant standard of care pharmacologic therapy for chronic HF, echocardiography was used to assess effects on cardiac function. An independent analysis by Duke Clinical Research Institute suggested that the highest dose of elamipretide (0.25 mg/kg/hr administered intravenously over 4 hours) significantly improved mean left ventricular (LV) end systolic volume (absolute change from baseline -11.1 mL versus 1.5 mL for placebo; mean difference = -12.6 mL; p=.0157) and mean LV end diastolic volume (absolute change from baseline -17.9 mL versus 2.9 mL for placebo; mean difference = -20.8 mL; p=.002) at the end of the infusion. These changes occurred in the absence of any heart rate or blood pressure change. These findings, after a single dose of elamipretide, are suggestive of a beneficial effect and require further investigation with repeat dosing.

4.2.2. Potential Risks

4.2.2.1. Safety findings – Nonclinical studies

Toxicology studies in rats and dogs showed that elamipretide has an acceptable profile that permits clinical investigations in humans for the proposed duration of the study.

In rats and dogs, no safety issues relevant to either IV infusion or SC administration at therapeutic doses were identified during the nonclinical evaluation of elamipretide. Elamipretide did not cause end-organ toxicity at any dosage tested in either rats or dogs. Systemic toxicity at high doses was manifested primarily by acute and transient clinical signs, which may have been mediated by histaminergic-like reactions. Effects were associated with maximum elamipretide plasma concentration (C_{max}) and were rapidly reversible as plasma concentrations of elamipretide and histamine decreased. Dose administration was not associated with any adverse effects on cardiovascular, respiratory or central nervous system function; off-target non-adverse effects were limited to transient decrease of blood pressure and increase in heart rate, which is thought to be consistent with histaminergic-like reactions. In all studies, the severity of the effects was proportional to C_{max} for elamipretide; thus, the safety margin is estimated based on C_{max}, and not area under the plasma-concentration-time curve (AUC). The plasma elamipretide threshold

concentration for clinically-relevant adverse effects appears to be ~20,000 ng/mL in both rats and dogs, which is more than 10-fold higher than the maximum anticipated human exposures. Local injection site reactions evident upon SC administration varied with species, dose and dose concentration. In rats, it was determined that 40 mg/day and 40 mg/mL, respectively, were well tolerated.

Elamipretide was negative for genotoxicity in the full battery of tests and caused no significant hemolysis or inhibition of receptor binding. Elamipretide was not associated with adverse effects on fertility or embryo-fetal development.

No formal immunotoxicity studies have been performed. As a tetrapeptide the immunogenic potential of the drug is expected to be low.

4.2.2.2. Human safety

The safety profile of multiple SC doses of elamipretide has not yet been evaluated in HF patients. Single elamipretide doses up to 1 mg/kg administered IV over 4 hours were safe and well-tolerated in 24 patients with stable CHF in a Phase 1 trial. No SAEs or deaths were recorded. A total of four TEAEs were reported in three elamipretide-treated subjects: worsening renal failure, dyspnea, tachycardia, and low hemoglobin. These events were assessed by the investigator to be of mild or moderate in severity and unrelated to study medication.

In 7 completed single-dose IV trials in healthy subjects, the most commonly reported treatment emergent adverse events (TEAEs) in subjects dosed with MTP 131 were headache, nausea, and hyponatremia. Across the 3 trials evaluating single IV doses of elamipretide in cardio-renal patient populations (i.e., chronic HF, acute kidney injury, and acute coronary syndrome), single IV doses of elamipretide were generally safe and well tolerated with no notable differences between the elamipretide and placebo treatment groups in the frequency or severity of adverse events.

Both single-dose SC administration and multiple-dose SC administration for seven days were well tolerated in healthy adult subjects. No deaths or drug-related SAEs occurred, and no subjects withdrew from the study for drug-related reasons. The most commonly reported TEAE in the elamipretide treatment group was mild injection site pruritus, reported with similar frequency after single and multiple doses.

4.2.3. Conclusions

In summary, based on the clinical and non-clinical study data, acceptable safety risks are expected for the proposed current study. Visiting Nurses will visit subjects daily to administer study medication and therefore subjects will have an opportunity to report any safety concerns on a daily basis. Hence the benefit:risk ratio of this study is considered favorable.

5. OBJECTIVES

5.1. Primary Objective

To evaluate the effects of multiple subcutaneous (SC) doses of elamipretide on left ventricular end systolic volume (LV ESV) assessed by cardiac Magnetic Resonance Imaging (MRI).

5.2. Secondary Objective

- To evaluate the safety and tolerability of multiple SC doses of elamipretide
- To evaluate the effects of multiple SC doses of elamipretide on LV systolic and diastolic function, LV volumes, LV global longitudinal strain, left atrial (LA) volume, LV mass, mitral and tricuspid regurgitation severity, and right ventricular (RV) function.

5.3. Exploratory Objectives

To evaluate the effects of multiple SC doses of elamipretide on:

- 6-minute walking distance
- Quality of life
- NT-pro-BNP levels
- Borg dyspnea scale

6. INVESTIGATIONAL PLAN

6.1. Study Design

This is a randomized, double-blinded, placebo-controlled, multiple dose Phase 2 study in subjects with stable heart failure with reduced ejection fraction (HFrEF). Subjects will go through three distinct periods during the study:

Screening Period: The Screening Period will begin with the signature of the informed consent form (ICF) and will last up to 28 days. During the Screening Period, subjects will undergo screening procedures as described in the Study Schedule (see Attachment 1) to determine their eligibility for the study. Screening procedures may be completed over more than 1 day during the Screening Period, so long as all procedures are completed within the Screening Period. Subjects who meet all study requirements, including all inclusion and none of the exclusion criteria, as well as confirmation by an independent MRI core lab of at least 3 viable LV segments (hyperenhancement ≤ 25%) may enter the Treatment Period.

Treatment Period: The Treatment Period will begin on the day of the Baseline Visit, which will be defined as Study Day 1. At the Baseline Visit, subjects will undergo Baseline procedures as described in the Study Schedule (see Attachment 1). Subjects who continue to meet eligibility criteria will enter the Treatment Period. Subjects will be administered study medication by subcutaneous (SC) injection at the Study Center on Days 1 through 3 and will receive instruction on scheduling daily visits with a Visiting Nurse to inject study medication SC on a daily basis (except for study visit days) for the remainder of the Treatment Period. The subject will return to the study center for assessments and administration of study medication at the Weeks 1 and 2 Visits. Subjects will receive the last dose of study medication on the day prior to the Week 4 Visit, when the Treatment Period will conclude.

Follow-Up Period: The Follow-Up Period will begin after completion of the Week 4 Visit and will last for 14 days. Subjects will return to the Study Center for a visit at Week 6 for final safety and efficacy assessments, as described in the Study Schedule (see Attachment 1).

6.2. Study Schedule

Study procedures and their timing are summarized in the Study Schedule (Attachment 1). A list of all clinical laboratory tests to be performed is found in Attachment 2.

6.2.1. Screening Period: Day -28 to Day -1

- Informed Consent Form will be reviewed and signed
- Demographics will be recorded (age, gender, ethnicity, race)
- All inclusion and exclusion criteria will be reviewed

A three-step screening procedure will be performed:

STEP 1:

- Relevant medical history will be taken, including a detailed treatment history
- Documentation of concomitant medication (including supplements and vitamins)

- Cardiovascular physical examination including height (as described in Section 6.3.1)
- 12-lead resting Electrocardiogram (ECG)
- Vital signs will be recorded (as described in Section 6.3.3): temperature, heart rate, respiration rate and blood pressure, recorded in the sitting position after at least 10 minutes rest
- 2-D echocardiography will be used to assess LVEF and LVEDD indexed to Body Surface Area (BSA).

STEP 2:

If the subject qualifies for the study after Step 1, the following assessments will be conducted:

- Blood drawn for local clinical laboratory testing as outlined in Attachment 2
- Women of child-bearing potential will have a serum pregnancy test performed
- Urine will be sampled for analysis

STEP 3:

If the subject qualifies for the study after both Step 1 and Step 2, the subject will undergo a delayed gadolinium-enhanced cardiac MRI evaluation to evaluate eligibility and to determine the number of viable LV segments. At the discretion of the Investigator, local clinical laboratory testing may be repeated prior to the MRI if there is concern of changes to subject eligibility. The images will be sent to the cardiac MRI core lab for an assessment of suitability for study entry.

6.2.2. Treatment Period: Study Visits

6.2.2.1. Day 1 (Baseline)

Subjects who have been deemed eligible during the Screening Period will return for randomization and the following procedures will be performed:

Before Study Medication Injection

- All inclusion and exclusion criteria will be reviewed
- Review of the relevant medical history since the Screening Visit
- Documentation of AEs that are related to a study procedure and/or meet seriousness criteria that occurred since the signing of the informed consent form as outlined in Section 9.7.2.
- Documentation of concomitant medication (including supplements and vitamins)
- Cardiovascular physical examination (as described in Section 6.3.1)
- 12-lead resting ECG (as described in Section 6.3.4)
- Vital signs (as described in Section 6.3.3)
- Blood drawn for clinical laboratory testing and NT-pro-BNP as outlined in Attachment 2
- Urine will be sampled for analysis (as described in Section 6.3.9.3)

- Women of child-bearing potential will have a urine pregnancy test performed
- 2-D and 3-D echocardiography
- 6-Minute Walk Test (as described in Section 6.3.7 and as outlined in Attachment 3)
- Kansas City Cardiomyopathy Questionnaire (KCCQ) (as described in Section 6.3.2 and as outlined in Attachment 4)
- Borg dyspnea scale
- Blood drawn for plasma analysis of elamipretide and metabolites (pre-dose) (as described in Section 6.3.9.5)
- Study medication injection

After Study Medication Injection

- Injection site reaction (ISR) assessments (as described in Section 6.3.10)
- Blood drawn for plasma analysis of elamipretide and metabolites (45 minutes post-injection ±15 minutes) (as described in Section 6.3.9.5)

6.2.2.2. Week 1 (Day 8 + 3 days)

The following evaluations will be performed:

- Documentation of concomitant medications (including supplements and vitamins)
- Documentation of AEs
- Cardiovascular physical examination
- Vital signs
- 12-lead resting ECG
- Blood drawn for clinical laboratory and NT-pro-BNP
- Blood drawn for plasma analysis of elamipretide and metabolites (pre-dose and 45 minutes post-injection ±15 minutes)
- Study medication injection
- ISR assessments
- Cardiac MRI approximately 1 to 6 hours post-injection
- Please note that on days 1 through 3 patients have to return to the site for the administration of the IMP as well as the assessment of injection site reactions

6.2.2.3. Week 2 (Day 15 ± 3 days)

The following evaluations will be performed:

- Documentation of concomitant medications (including supplements and vitamins)
- Documentation of AEs

- Cardiovascular physical examination
- Vital signs
- 12-lead resting ECG
- Blood drawn for clinical laboratory testing and NT-pro-BNP
- Blood drawn for plasma analysis of elamipretide and metabolites (pre-dose and 45 minutes post-injection ±15 minutes)
- Study medication injection
- ISR assessments

6.2.2.4. Week 4 (Day 29 + 3 days)/Early Discontinuation Visit

The following evaluations will be performed:

- Documentation of concomitant medication (including supplements and vitamins)
- Documentation of AEs
- Cardiovascular physical examination
- 12-lead ECG
- Vital signs will be recorded
- Blood drawn for clinical laboratory testing and NT-pro-BNP
- Blood drawn for plasma analysis of elamipretide and metabolites
- Urine will be sampled for analysis
- Women of child-bearing potential will have a urine pregnancy test performed
- 2-D and 3-D echocardiography
- Cardiac MRI
- KCCQ
- Borg dyspnea scale
- 6-Minute Walk Test

6.2.3. Follow-up Period

6.2.3.1. Week 6 (Day 43 ± 3 days)

The following evaluations will be performed:

- Documentation of concomitant medication (including supplements and vitamins)
- Documentation of AEs
- Cardiovascular physical examination
- Vital signs

- 12-lead resting ECG
- Blood drawn for clinical laboratory testing and NT-pro-BNP levels
- Blood drawn for plasma analysis of elamipretide and metabolites
- 2-D and 3-D echocardiography
- Subject will conclude the study

6.3. Study Assessments

The following section describes study assessments occurring during the study. Study assessments and procedures are presented by study visit in Attachment 1. Details regarding clinical laboratory tests are found in Attachment 2.

6.3.1. Relevant Medical History and Cardiovascular Physical Examination

At the Screening Visit, a relevant medical history (including medication and procedure history, smoking history, heart failure etiology, and concomitant medication) will be taken.

At the Day 1 visit, a review of the relevant medical history (including concomitant medication and procedures) since the Screening visit will be taken.

At all visits, a cardiovascular physical examination including lung auscultation and weight will be performed. Height will only be measured at the Screening Visit.

6.3.2. Kansas City Cardiomyopathy Questionnaire (KCCQ)

KCCQ will be performed according to the standardized questionnaire at the Day 1 and Week 4 visits. The KCCQ instructions are provided in Attachment 4.

6.3.3. Vital signs

During all site study visits, the vital signs measurements will include temperature, heart rate, respiration rate and blood pressure, recorded in the sitting position after at least 10 minutes rest. At Day 1 these vital signs measurements will be performed as part of the study eligibility confirmation.

6.3.4. Electrocardiograms (ECGs)

A 12-lead resting ECG will be obtained in the supine position at all study visits.

ECG intervals (PR, QRS, QT, QTc), heart rate and ECG findings will be recorded for each subject. Based on signs or symptoms, additional 12-lead ECGs may be performed.

6.3.5. Echocardiogram

At the Screening Visit, a 2-D echocardiographic screening evaluation of LVEF and LV end-diastolic dimension (LVEDD) will be performed.

At Day 1, Week 4, and Week 6 visits, both 2-D and a 3-D echocardiograms will be performed to assess parameters of LV systolic and diastolic function, global longitudinal strain, LA volume, LV mass, mitral and tricuspid regurgitation severity, and RV function.

Detailed specifications of the echocardiogram procedures and image assessments are presented in the Study Echocardiography Manual.

6.3.6. Cardiac MRI

At the Screening Visit, subjects who qualify after initial Step 1 screening evaluations will undergo a delayed gadolinium-enhanced cardiac MRI. The screening evaluation of the number of viable segments will be performed by an independent cardiac MRI core lab that will decide if subjects are eligible for inclusion. At the Week 1 and Week 4 visits, subjects will undergo a cardiac MRI examination, to evaluate LV cardiac volumes and function. At the Week 1 visit, the cardiac MRI examination will occur at approximately 1 to 6 hours post-dose.

Detailed specifications of the MRI procedures and image assessments are presented in the Study MRI Manual.

6.3.7. Borg Dyspnea Scale

Borg dyspnea scale will be assessed at Day 1 (baseline) and Week 4 visits. The instructions are provided in Attachment 7

6.3.8. 6-Minute Walk Test (6MWT)

At the Day 1 and Week 4 visits, the distance walked (in meters) during the 6MWT will be recorded. The Day 1 6MWT should be completed prior to study medication administration. The 6MWT instructions are provided in Attachment 3.

6.3.9. Clinical Laboratory Testing

Sample collection, processing and handling details are provided in the Laboratory Manual.

6.3.9.1. Blood chemistries

The following blood chemistries will be carried out at all study visits: sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine (and eGFR calculated with the MDRD Study equation), total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), calcium, albumin, total protein, hsTroponin I, venous blood glucose, and triglycerides.

6.3.9.2. Hematology

The following parameters will be determined on all study visits: hemoglobin, hematocrit, erythrocyte count (RBC), leukocytes (WBC), segmented neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelets.

6.3.9.3. Urinalysis

Urinalysis will be sampled at the Screening Visit, Day 1, and Week 4 and will include: urine specific gravity, pH, protein, microalbuminuria, glucose, ketones, blood, sodium, chloride, and creatinine.

6.3.9.4. Pregnancy tests

Women of child-bearing potential will have a serum pregnancy test performed at the Screening Visit. Women of child-bearing potential will have a urine pregnancy test on Day 1 and Week 4. The results of the Day 1 pre-dose pregnancy test must be evaluated before randomization to ensure eligibility.

6.3.9.5. Samples for elamipretide and metabolite plasma levels

Blood samples for PK determinations of elamipretide and metabolites (M1, M2) concentrations will be collected before administration of study medication and at 45 minutes ±15 minutes post-dose at the Day 1, Week 1 and Week 2 visits, and at any time point at the Week 4 and Week 6 visits.

Please refer to the Laboratory Manual and the Pharmacy Manual for specific details of sample handling, preparation, and shipping instructions.

6.3.9.6. Exploratory biomarkers

Blood samples for determination of NT-pro-BNP will be collected on all study visits from Day 1 through Week 6 prior to administration of study medication.

6.3.10. Injection Site Reaction (ISR) Assessments

During the 4-week treatment period, injection site reactions will be assessed on a daily basis to better characterize subcutaneous administration. Two assessments will occur after each injection:

1. Subjects will complete the ISR self-assessment questionnaire (see Attachment 5) at approximately 15 minutes post-injection. The questionnaire assesses how bothered the patient was following study medication injection. The responses to the ISR self-assessment questionnaires will be reviewed by the Investigator (or designee) at each on-site visit. Any injection site reaction reported by the subject and determined to be clinically significant by the Investigator, regardless of whether it is captured as part of this assessment, should be reported as an AE.
2. At each home visit, the Visiting Nurse will assess the current day's injection site. At Days 1 through 3, Week 1 and Week 2 visits, the Investigator (or designee) will assess the current day's injection site. The assessment will evaluate erythema, pain, swelling, and pruritus at approximately 15 minutes post-injection. If any reaction is apparent, the injection site will also be evaluated at 30 minutes post-injection.

Injection site reactions determined to be adverse events by the Investigator should be graded according to the guidelines detailed in Attachment 6.

7. STUDY POPULATION

The inclusion and exclusion criteria for participation in this study are provided below. All screening procedures must be completed during the Screening period, but may be performed on different days. Screening procedures cannot be repeated, and subjects cannot be re-screened without the Sponsor's approval. If a subject is re-screened, they will maintain their original screening number. Subjects may only be enrolled into the study one time.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

7.1. Inclusion Criteria

A subject must meet all of the following criteria prior to Study Day 1 to be eligible for inclusion in the study:

1. Willing and able to provide signed informed consent form (ICF) prior to participation in any study-related procedures.
2. Age ≥40 and ≤80 years.
3. A known history of chronic ischemic or non-ischemic cardiomyopathy of at least 6 months duration from the time of the initial diagnosis or signs and symptoms consistent with heart failure..
4. Receiving heart failure (HF) treatment, including, but not limited to, angiotensin converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB), and an evidence-based beta blocker for the treatment of HF. Subjects who cannot tolerate ACEI or ARB due to reduced renal function or hypotension are eligible. Subjects may be receiving aldosterone antagonists, but this is not a requirement for the study.
5. HF is considered to be stable in the judgment of the Investigator AND doses of HF treatment have been stable for at least 1 month prior to the Screening Visit.
6. In normal sinus rhythm (electrocardiogram documented) at Screening and Day 1 and no history of atrial fibrillation in the past 12 months
7. No hospitalization related to HF within 1 month prior to the Screening Visit.
8. Left Ventricular Ejection Fraction (LVEF) ≤ 40% by 2-D echocardiography at Screening.
9. At least 3 viable segments (hyperenhancement ≤ 25%) by a qualifying delayed gadolinium-enhanced cardiac MRI examination at Screening (confirmed by independent core lab).
10. Willing to adhere to the study requirements for the length of the trial.
11. Women of childbearing potential must agree to use 1 of the following methods of birth control from the date they sign the ICF until two months after the last dose of study medication:
    a. Abstinence, when it is in line with the preferred and usual lifestyle of the subject. Subject agrees to use an acceptable method of contraception should they become sexually active.

b. Maintenance of monogamous relationship with a male partner who has been surgically sterilized by vasectomy (the vasectomy procedure must have been conducted at least 60 days prior to the Screening Visit or confirmed via sperm analysis).

c. Barrier method (e.g., condom or occlusive cap) with spermicidal foam/gel/film/cream AND either hormonal contraception (oral, implanted, or injectable) or an intrauterine device or system.

d. Note: Non-childbearing potential is defined as surgical sterilization (e.g., bilateral oophorectomy, hysterectomy, or tubal ligation) or postmenopausal (defined as permanent cessation of menstruation for at least 12 consecutive months prior to the Screening Visit).

7.2. Exclusion Criteria

A subject who meets any of the following criteria at Screening will be excluded from the study:

1. History of any concurrent medical condition which, in the opinion of the Investigator, significantly increases the potential risks associated with administration of study medication or any other aspect of study participation.
2. Any contraindication to MRI scanning as assessed by local MRI safety questionnaire, which may include:
    a. History of intra-orbital metal fragments which have not been removed
    b. Severe claustrophobia
    c. Non-MRI safe cochlear implant(s) or intracranial aneurysm clips
    d. Extensive tattoos located on the torso that contain metallic inks
    e. Other non-removable implanted metallic or electronic devices that have not been determined to be MRI safe
    f. Inability to lie flat
3. Inadequate echocardiogram image quality (defined as poor sound transmission and/or < 10 endocardial segments seen).
4. LVEDD indexed to Body Surface Area is > 45 mm/m^2 assessed by 2-D echocardiography.
5. Coronary or peripheral revascularization procedures, valvular procedures, OR any major surgical procedure within 3 months prior to the Screening Visit.
6. Acute coronary syndrome, stroke or transient ischemic attack (TIA) within 3 months prior to the Screening Visit.
7. Obstructive or restrictive cardiomyopathy, infiltrative diseases of the myocardium (e.g., amyloid, sarcoid, etc.) myocarditis, or reductions in LV function thought to be secondary primarily to valvular heart disease, prior cardiac valve surgery or known aortic stenosis.

8. The presence or anticipated placement of any pacemaker, implantable cardioverter defibrillator (ICD), or cardiac resynchronization therapy (CRT) devices during the ensuing 6-week study period.
9. Presence of second degree or advanced heart block.
10. Uncontrolled hypertension defined as a systolic blood pressure > 160 mmHg or a diastolic blood pressure > 110 mmHg on at least two consecutive readings.
11. Presence of any left ventricular thrombus, pericardial disease, uncorrected thyroid disease or a dyskinetic left ventricular aneurysm.
12. History of cancer that causes symptoms, disabilities, or is likely to lead to hospitalization or treatment in the next 12 months.
13. Currently receiving treatment with chemotherapeutic agents or immunosuppressant agents or has received prior radiation therapy to the chest.
14. Liver enzymes (alanine aminotransferase [ALT] AND/OR aspartate aminotransferase [AST]) elevation > 3 times the upper limit of normal (ULN).
15. Total bilirubin > 1.5 times ULN in the absence of Gilbert's Syndrome.
16. Bleeding diathesis or any known blood dyscrasia.
17. Anemia, defined as hemoglobin < 9 g/dL or planned blood transfusions in the next 6 weeks.
18. Estimated glomerular filtration rate (eGFR) < 30 mL/min, using the Modification of Diet in Renal Disease (MDRD) Study equation:
    a. eGFR (mL/min/1.73 m2) = $175 \times (Scr)^{-1.154} \times (Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American)
19. History of hepatitis B, hepatitis C or Human Immunodeficiency Virus (HIV) infection, or diagnosis of immunodeficiency.
20. Known active drug or alcohol abuse within 1 year of the Screening Visit. Alcohol abuse is defined as 15 or more drinks for men per week or 8 or more for women.
21. Recipient of any investigational drugs, stem cell or gene therapies, or devices OR participation in another clinical trial, within 3 months prior to the Screening Visit.
22. Any significant acute or chronic medical or psychiatric illness that, in the judgment of the Investigator, could compromise the subject's safety, limit subject's ability to complete the study, and/or compromise the objectives of the study.
23. Female subjects who are pregnant, planning to become pregnant, or lactating.
24. Currently requiring any changes in doses of cardiovascular medication (including diuretics) in order to control worsening of HF symptoms.
25. Known allergy to gadolinium.

26. Currently receiving treatment with therapeutic doses of anticoagulants. Antiplatelet therapy used to prevent cardiovascular disease (primary prevention) or to treat chronic disease (secondary prevention) is permitted, as well as vitamin K antagonists.
27. Currently receiving treatment with sacubitril/valsartan or trimetazidine.

7.3. Prohibited Medications

The use of any other investigational drug except elamipretide is prohibited during the conduct of the current trial.

The use of therapeutic doses of anticoagulants (not including antiplatelet therapy used to prevent cardiovascular disease [primary prevention] or to treat chronic disease [secondary prevention]), sacubitril/valsartan, trimetazidine, chemotherapeutic or immunosuppressant medications is prohibited in this study. No additional medications are prohibited per protocol. All concomitant medications will be recorded in the source data and the Electronic Case Report Form (eCRF). Changes in dosages of current therapeutic agents during the conduct of the study will be discouraged, unless required to treat an Adverse Event.

7.4. Discontinuations

7.4.1. Discontinuation of Subjects

Subjects may be discontinued for the following reasons:

- Investigator Decision
    - The Investigator decides that the subject should be discontinued from the study for any reason.
- Subject Decision
    - The subject or the subject's designee, (e.g., parents or legal guardian), requests to be withdrawn from the study.
        - Subjects who withdraw should be explicitly asked about the contribution of possible adverse events to their decision to withdraw consent, and any adverse event information elicited should be documented.
        - Preferably the subject should withdraw consent in writing and, if the subject or the subject's representative refuses or is physically unavailable, the site should document and sign the reason for the subject's failure to withdraw consent in writing.
    - The subject is lost to follow-up after a reasonable number of attempts to contact the subject (including documented phone calls and/or emails, and a certified letter) have been completed.
- Sponsor Decision
    - The Sponsor or its designee stops the study or stops the subject's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP guidelines.

- Adverse Event
    - If the Investigator decides that the subject should be withdrawn because of an AE or a clinically significant laboratory value, the investigational product is to be discontinued and appropriate measures are to be taken. The Sponsor or its designee is to be alerted immediately.

Any subject withdrawing from the study will be asked to complete the Early Discontinuation visit assessments (see Attachment 1).

7.4.2. Discontinuation of Study Sites

Study site (research center) participation may be discontinued if the Sponsor or its designee, the Investigator, or the Ethics Committee (EC) of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP guidelines.

7.4.3. Discontinuation of the Study

The study will be discontinued if the Sponsor or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP guidelines.

8. TREATMENT

8.1. Treatments Administered

Approximately 70 subjects will receive study medication administered as a single daily subcutaneous (SC) injection containing either 4 mg elamipretide, 40 mg elamipretide, or placebo for 4 consecutive weeks. Study medication will be administered daily to the subject in the abdomen (rotating clockwise around the four abdominal quadrants) by either the clinical site staff or a Visiting Nurse. Subjects will be instructed to take their background heart failure medication at approximately the same time every day during the 4 week treatment period. At the Day 1 visit, study medication injection will occur after completion of several baseline procedures (see Section 6.2.2.1). A few assessments will be completed after study medication injection on Day 1. Study medication injection and evaluation on Days 2 through 3 will occur at the study site. Starting on Day 4, subjects will be instructed to schedule the daily Visiting Nurse visits at approximately the same relative time each day. If, in the opinion of the Visiting Nurse or the clinical site staff, it is more appropriate to administer the medication in another body area judged appropriate for a SC injection, he/she may do so at his/her discretion, provided that it is at least 5 cm from the previous day's location of administration. At each home visit, in addition to the subject completing the ISR self-assessment questionnaire, the Visiting Nurse will assess the current day's injection site. At Days 1 through 3, Week 1 and Week 2 visits, the Investigator (or designee) will assess the current day's injection site. The assessment will evaluate erythema, pain, swelling, and pruritus at the injection site at approximately 15 minutes post-injection. If any reaction is apparent, the injection site will also be evaluated at 30 minutes post-injection.

Injection site reactions determined to be adverse events by the Investigator should be graded according to the guidelines detailed in Attachment 6.

8.2. Materials and Supplies

Study medication (elamipretide and placebo) will be dispensed, stored, and administered according to the Pharmacy Manual.

8.2.1. Elamipretide

Elamipretide (MTP-131) drug product will be provided as a sterile solution for administration by SC injection. Each single-use vial is filled with one milliliter of drug product containing the equivalent of 40 mg elamipretide, added as MTP-131 acetate, in an isotonic, unpreserved, clear, colorless solution.

8.2.2. Placebo

The placebo for this trial will be provided as a sterile solution in matching sterile glass vials and is composed of the excipients used to manufacture the investigational drug elamipretide without the active drug substance. The placebo will be handled and administered identically as active drug. Subjects randomized to placebo will receive an injection containing either 1 mL or 0.1 mL of sterile solution to match the two volumes administered in the active arm.

8.3. Treatment Logistics and Accountability

All drug accountability records must be kept current, and the Investigator must be able to account for all used and unused vials of study medication. These records should contain the dates, quantity, and study medication:

- Received at site
- Administered to each subject,
- Dispensed to each subject,
- Returned from each subject, and
- Disposed of at the site or returned to the Sponsor or designee

The clinical monitor responsible for the study site will provide written approval for the destruction or return of unused study medication vials following reconciliation of all clinical supplies.

8.4. Method of Assignment to Treatment and Randomization

At Day 1, after eligibility criteria have been confirmed, a treatment kit number will be assigned to each subject on the basis of a centralized computer-generated randomization schedule. Subjects will be randomized into 1 of 3 treatment groups in a 1:1:1 fashion to receive either elamipretide 4 mg, elamipretide 40 mg, or placebo, so that a target of at least 22 subjects will be randomized to the elamipretide 4 mg dose group, 22 subjects will be randomized to the elamipretide 40 mg dose group, and 22 subjects will be randomized to the placebo treatment group. Treatment kits for placebo will specify injection volumes of either 0.1 or 1 mL in order to maintain the blind.

8.5. Rationale for Selection of Doses in the Study

The doses and route of administration (i.e., 4 mg in 0.1 mL and 40 mg in 1.0 mL via SC injection) for the current study have previously been tested in a clinical trial involving healthy subjects. Single IV doses ranging from 0.02 mg/kg to 1 mg/kg have been tested in subjects with stable HF. The doses for the current study were chosen based on the systemic exposure profile, as well as the safety observed in previous clinical trials.

The plasma elamipretide threshold concentration for clinically-relevant adverse effects appears to be ~20,000 ng/mL in both rats and dogs, which is more than 10-fold higher than the maximum anticipated human exposures. In healthy human adults, systemic exposure (in terms of mean $AUC_{0-\tau}$ on Day 7) to elamipretide following repeat SC injection at 40 mg in 1 mL was 3,810 ng·h/mL, while mean C_{max} on Day 7 was 1,320 ng/mL. No accumulation of elamipretide was seen following repeat dosing for seven consecutive days. Neither metabolite of elamipretide (M1 and M2) is active or implicated in toxicology.

In a completed Phase 1 trial (SPISC-101), elamipretide given SC to healthy volunteers at doses up to 40 mg in 1 mL once daily for seven consecutive days was well tolerated, with no systemic safety issues. Local injection site reactions were limited to transient, local erythema and occasional pruritus or swelling, which resolved quickly without sequelae and without intervention.

Elamipretide demonstrated an acceptable safety and tolerability profile with single IV infusions of up to 1 mg/kg administered over 4 hours in subjects with stable HF in a completed Phase 1 trial (SPIHF-101).

8.6. Continued Access to Investigational Medicinal Product

Elamipretide will not be made available to study subjects after the conclusion of the study.

8.7. Blinding and Unblinding Procedures

The Sponsor, study personnel, and subjects will be blinded to treatment until the database is locked.

The Investigator will contact the Sponsor prior to unblinding any subject's treatment assignment unless in the instance of a medical emergency.

In case of an immediate medical emergency or if directed by the Sponsor, and only if the information is required by the Investigator to manage a subject's AE, is a subject's treatment assignment to be unblinded prematurely. In cases of medical emergency, the Investigator may unblind a subject's treatment assignment using the computerized system according to the instructions received. The Sponsor must be notified as soon as possible regarding the reason for unblinding.

Whenever the treatment assignment of an individual subject is unblinded, the reason, and the date and time of the unblinding must be included in source documentation. The name of the individual who broke the blind must be included in the site's source documentation.

The Sponsor designated CRO will control and document, according to the appropriate Standard Operating Procedures, the disclosure of treatment assignments, and treatment identity. These procedures ensure that no blinded staff (CRO, site, Sponsor) will have premature access to the subjects' treatment assignments. As described above, specific Sponsor personnel will be unblinded during the trial and will have access to study data in an unblinded fashion before the data lock.

8.8. Treatment Compliance

During the treatment period, study medication will be administered by clinical site staff or Visiting Nurse. Injection times and locations will be recorded.

9. EFFICACY AND SAFETY EVALUATIONS AND APPROPRIATENESS OF MEASUREMENTS

Study procedures and their timing are summarized in Attachment 1 and in Attachment 2.

9.1. Efficacy Measures

9.1.1. Primary efficacy measure

- LV ESV assessed by MRI

9.1.2. Secondary efficacy measure

- LVEF and LV EDV assessed by MRI
- The following parameters by echocardiography:
    - E/A (ratio between early and late mitral inflow velocity),
    - E/e' (Ratio between early mitral inflow velocity and mitral annular early diastolic velocity)
    - LV EDV, LV ESV and biplane EF
    - LV global longitudinal strain
    - LA volume
    - LV mass
    - Mitral regurgitation severity
    - Tricuspid regurgitation severity
    - RV fractional area change
    - RV systolic pressure (RVSP)

9.1.3. Exploratory efficacy measures

- Distance walked (meters) during 6MWT.
- Levels of NT-pro-BNP
- KCCQ score
- Borg dyspnea scale

9.2. Safety Evaluations

The safety and tolerability end-points will be assessed by:

- AEs
- Changes from baseline in vital signs
- Changes from baseline in electrocardiograms (ECGs)
- Changes from baseline in clinical laboratory evaluations

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting Sponsor or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

The Investigator is responsible for the appropriate medical care of subjects during the study.

The Investigator remains responsible for following, through an appropriate health care option, of AEs that are serious, considered related to the study treatment or the study, or that caused the subject to discontinue before completing the study. The subject should be followed until the event is resolved or explained.

The safety profile of elamipretide will be assessed through the recording, reporting, and analyzing of AEs, clinical evaluations, and laboratory tests.

Comprehensive assessment of any apparent toxicity experienced by study subjects will be performed throughout the course of the study, from the time of the subject's signature of informed consent. Study site personnel will report any AE, whether observed by the Investigator or reported by the subject. The reporting period for AEs is described in Section 9.7.2.

9.2.1. Adverse Events

An AE is defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerge or worsen relative to baseline during administration of an investigational medicinal product (IMP), regardless of causal relationship.

Adverse Events may include the following:

- Suspected adverse drug reactions: side effects known or suspected to be caused by the study medication.
- Other medical experiences, regardless of their relationship with the study medication, such as injury, surgery, accidents, extensions of symptoms or apparently unrelated illnesses, and significant abnormalities in clinical laboratory values, psychological testing, or physical examination findings.
- Events occurring as a result of protocol interventions (pre- or post-IMP administration)
- Reactions from study medication overdose, abuse, withdrawal, sensitivity, or toxicity. The Sponsor has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent.

9.3. Pre-Treatment Events

Untoward events and/or incidental diagnoses that occur prior to study medication administration are by definition, unrelated to the study medication. Pre-treatment events or incidental diagnoses will be recorded on the past medical history electronic case report form (eCRF). However, if a pre-treatment event is assessed by the Investigator as related to a study procedure and/or meets seriousness criteria, it will be recorded as an AE on the AE eCRF, processed, and followed accordingly.

9.4. Baseline Medical Conditions

Those medical conditions related to the disease under study whose changes during the study are consistent with natural disease progression, or which are attributable to a lack of clinical efficacy of the study medication, are NOT considered as AEs and should not be recorded as such in the eCRF. These are handled in the efficacy assessments and should be documented on the medical history page of the eCRF.

Baseline medical conditions, not in the therapeutic area of interest/investigation, that worsen in severity or frequency during the study should be recorded and reported as AEs.

9.5. Abnormal Laboratory and Other Abnormal Investigational Findings

Abnormal laboratory findings and other objective measurements should NOT be routinely captured and reported as AEs. However, abnormal laboratory findings or other objective measurements should be reported on the AE pages of the eCRF that:

- meet the criteria for a SAE
- result in discontinuation of the IMP
- require medical intervention or
- are judged by the Investigator to be clinically significant changes from baseline

When reporting an abnormal laboratory finding on the AE pages of the eCRF, if available, a clinical diagnosis should be recorded rather than the abnormal value itself (for example, “anemia” or “decreased red blood cell count” rather than “hemoglobin = 10.5 g/dL”).

9.6. Serious Adverse Events

A serious adverse event (SAE) is any AE from this study that:

- Results in death. In case of a death, the cause of death is used as the AE term, and the fatality is considered as the OUTCOME.
- Is life-threatening. The term “life-threatening” refers to a SAE in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is otherwise considered medically important.

Important medical events may be considered as SAEs when, based upon medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered an SAE and all such cases should be reported in an expedited manner as described in Section 9.8.

9.6.1. Events that Do Not Meet the Definition of a Serious Adverse Event

Elective hospitalizations to simplify study treatment or study procedures (e.g., an overnight stay) are not considered as SAEs. However, all events leading to unplanned hospitalizations (not documented prior to ICF signing) or unplanned prolongation of an elective hospitalization (e.g., undesirable effects of any administered treatment) must be documented and reported as SAEs.

9.7. Recording of Adverse Events

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be recorded on an ongoing basis in the appropriate section of the electronic Case Report Form (eCRF). Among these AEs, all serious AEs must be additionally documented and reported using the study specific SAE Report Form.

It is important that each AE report include a description of the event along with the duration (onset and resolution dates), severity, relationship to study medication, potential causal factors, treatment given or other action taken (including dose modification or discontinuation of the IMP), and the outcome.

As the quality and precision of acquired AE data are critical, Investigators should use the AE definitions provided and should observe the following guidelines when completing the AE pages of the eCRF:

- Whenever possible, recognized medical terms should be used to describe AEs rather than lay terms (for example, “influenza” rather than “flu”), and abbreviations should be avoided.
- Adverse events should be described using a specific clinical diagnosis, if available, rather than a list of signs or symptoms (for example, “congestive heart failure” rather than “dyspnea, rales, and cyanosis”). However, signs and symptoms that are not associated with an identified disease or syndrome, or for which an overall diagnosis is not yet available, should be reported as individual AEs.
- Provisional diagnoses (e.g., “suspected myocardial infarction”) are acceptable, but should be followed up with a definitive diagnosis if later available. Similarly, a fatal event with an unknown cause should be recorded as “death of unknown cause.”
- In cases of surgical or diagnostic procedures, the condition or illness leading to the procedure is considered the AE rather than the procedure itself.

Adverse events occurring secondary to other events (e.g., sequelae or complications) should be identified by the primary cause. A primary AE, if clearly identifiable, generally represents the most accurate clinical term to record in the eCRF.

9.7.1. Investigator Assessments

9.7.1.1. Severity/Intensity

Investigators must assess the severity/intensity of AEs according to the following qualitative toxicity scale:

Mild: The subject is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning: the subject is unable to carry out usual activities.

Adverse events relating to injection reactions should be graded according to the guidelines detailed in Attachment 6.

9.7.1.2. Relationship to the Investigational Medicinal Product (IMP)

Investigators must systematically assess the causal relationship of AEs to the study medication using the following definitions (the decisive factor being the temporal relationship between the AE and administration of the study medication):

Probable: A causal relationship is clinically/biologically highly plausible, there is a plausible time sequence between onset of the AE and administration of the study medication, and there is a reasonable response on withdrawal.

Possible: A causal relationship is clinically/biologically plausible and there is a plausible time sequence between onset of the AE and administration of the study medication.

Unlikely: A causal relationship is improbable and another documented cause of the AE is most plausible.

Unrelated: A causal relationship can be excluded and another documented cause of the AE is most plausible.

9.7.2. Adverse Event Reporting Period

The AE reporting period begins when the subject signs the ICF and continues through the clinical study's post treatment follow-up period, defined as 14 days after last administration of study medication.

Note that AEs that occur between the time subject signs the ICF and the time the subject is dosed with study medication will be summarized in the medical history eCRF and not as an AE unless the event is assessed by the Investigator as related to a study procedure and/or meets the definition of an SAE. New protocol related AEs (caused by any intervention required by the protocol) and updates on all AEs ongoing or with an unknown outcome must be recorded until the last subject visit required by the protocol. A last batch of queries will be sent after last study visit if remaining ongoing/unknown outcomes of reported AEs are pending. After the last batch

of queries with all collected data have been fully processed, CRFs and database will no longer be updated.

However, SAEs and medically relevant ongoing/unknown outcome AEs will be followed-up until resolution or stabilization by the Sponsors Pharmacovigilance department. Beyond this defined reporting period, any new SAE spontaneously reported to the Sponsor by the Investigator would be collected and processed. Additional information on SAE, obtained after database lock, will reside solely in the safety database.

Within the study, all subjects who took at least 1 dose of IMP, whether they completed the treatment period or not, should enter the 14-day period as defined above.

If a subject is documented as lost-to follow-up, ongoing/unknown outcome AEs will not be followed-up.

For screening failure subjects, new AEs and updates must be recorded in the CRFs until the date the subject was determined to be a screen failure. Beyond that date, only SAEs and medically relevant AEs will be followed-up by the Sponsor's Pharmacovigilance group and all data will be housed within the safety database.

9.8. Serious Adverse Event Expedited Reporting

In the event an SAE occurs during the reporting period, the Investigator must immediately (within a maximum of 24 hours after becoming aware of the event) inform the Sponsor as detailed in the Clinical Trial Pharmacovigilance Procedural Manual.

For any SAE, the following minimum information is required as initial notification:

- Investigator/Reporter with full contact information
- Subject identification details (study number, site number, subject number)
- Study medication administration details (dose and dates)
- Event verbatim terms, a brief description of signs/symptoms/diagnosis and the date of onset
- Seriousness criteria(ion) met
- Relationship of the event to the study medication (eg, the causality according to the Investigator)

Reporting procedures and timelines are the same for any new follow-up information on a previously reported SAE.

All SAE reports must be completed as described in the eCRF completion guidelines and submitted through the Electronic Data Capture (EDC) system of the clinical database. Other relevant information from the clinical database (including demographic data, medical history, concomitant medication and study medication dosing information) will automatically be sent via the EDC system when the SAE form is submitted.

The names, addresses, telephone and fax numbers for SAE back-up reporting (paper), are included in the Safety Reporting Plan.

The Investigator/Reporter must respond to any request for follow-up information (e.g., additional information, outcome and final evaluation, specific records where needed) or to any question the Sponsor may have on the AE within the same timelines as described for initial reports. This is necessary to permit a prompt assessment of the event by the Sponsor and (as applicable) to allow the Company to meet strict regulatory timelines associated with expedited safety reporting obligations.

9.8.1. Pregnancy and Contraception

Any pregnancies must be reported to the Investigator in the two months after the last dose of study medication. In addition, women of childbearing potential must agree to use 1 of the following methods of birth control from the date they sign the ICF until two months after the last dose of study medication:

- Abstinence, when it is in line with the preferred and usual lifestyle of the subject. Subject agrees to use an acceptable method of contraception should they become sexually active.
- Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy (the vasectomy procedure must have been conducted at least 60 days prior to the Screening Visit or confirmed via sperm analysis).
- Barrier method (e.g., condom or occlusive cap) with spermicidal foam/gel/film/cream AND either hormonal contraception (oral, implanted, or injectable) or an intrauterine device or system.

Non-childbearing potential is defined as surgical sterilization (e.g., bilateral oophorectomy, hysterectomy, or tubal ligation) or postmenopausal (defined as permanent cessation of menstruation for at least 12 consecutive months prior to the Screening Visit).

For male subjects with female partners of child-bearing potential, highly effective methods of contraception must be adhered to prior to entry into the study and for at least 2 months after the last dose of study medication. Highly effective methods of contraception is defined as the usage by the female partner of any form of hormonal contraception or intra-uterine device (which should be established prior to the start of the study) plus usage by one of the partners of an additional spermicide-containing barrier method of contraception. Male subjects with pregnant partners must use a condom with spermicide from the start of treatment until at least 2 months after the last dose of study medication. Sperm or egg donation by patients is not permitted from the start of treatment until 2 months after the study medication was administered.

Only pregnancies considered by the Investigator as related to study treatment (e.g., resulting from an interaction between study medication and a contraceptive medication) are considered AEs unto themselves. However, all pregnancies with an estimated conception date that occurred during the AE reporting period, as defined in Section 9.7.2, must be recorded in the AE section of the eCRF. For this study, this applies to pregnancies in female subjects and in female partners of male subjects.

The Investigator must notify the Sponsor in an expedited manner of any pregnancy using the Pregnancy Form and the back-up reporting procedure as described in the Clinical Trial Pharmacovigilance Procedural Manual. Investigators must actively follow up, document, and report on the outcome of all pregnancies.

The Investigator must notify the Sponsor of these outcomes using Section II of the Pregnancy Form and submit the information using the back-up reporting procedure. Any abnormal outcome must be reported in an expedited manner as described in Section 9.8, while normal outcomes must be reported within 45 days from delivery.

In the case of an abnormal outcome, whereby the mother sustains an event, the SAE Report Form is required and will be submitted as described above.

9.8.2. Responsibilities to Regulatory Authorities, Investigators and Ethics Committees

The Sponsor will send appropriate safety notifications to regulatory authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs involving subjects to the EC that approved the study.

In accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) GCP guidelines, the Sponsor will inform the Investigator of findings that could adversely affect the safety of subjects, impact the conduct of the study, or alter the EC's approval/favorable opinion to continue the study. In particular, and in line with respective regulations, the Sponsor will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product (SUSARs). The Investigator should place copies of the safety reports in the Investigator site file. Country-specific regulations with regard to safety report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor will provide appropriate safety reports directly to the concerned lead IEC and will maintain records of these notifications. When direct reporting by the Sponsor is not clearly defined by country- or site- specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC of any safety reports provided by the Sponsor and or filing copies of all related correspondence in the site file.

For studies covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs will be carried out in accordance with that directive and with related guidances.

9.9. Appropriateness of Measurements

The measures used to assess safety in this study are consistent with those widely used and generally recognized as reliable, accurate, and relevant.

10. DATA QUALITY ASSURANCE

To ensure accurate, complete, and reliable data, the Sponsor or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate
- Sponsor start-up training to instruct the Investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- Make periodic visits to the study site
- Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- Review and evaluate eCRF data and use standard computer edits to detect errors in data collection
- Conduct a quality review of the database

In addition, the Sponsor or its representatives will periodically check a sample of the subject data recorded against source documents at the study site. The study may be audited by the Sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the study. If requested, the Investigator will provide the Sponsor, applicable regulatory agencies, and applicable ECs with direct access to original source documents.

10.1. Data Capture System

An electronic data capture system will be used in this study. The site will maintain a separate source for the data entered by the site into the Sponsor-provided electronic data capture system.

Case report form data will be encoded and stored in a clinical study database. Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system.

Any data for which paper documentation provided by the subject will serve, as a source document will be identified and documented by each site in that site's study file. Paper documentation provided by the subject may include, for example, a paper diary to collect subject reported outcome measures (e.g., a rating scale), a daily dosing schedule, or an event diary.

11. SAMPLE SIZE AND STATISTICAL METHODS

11.1. Determination of Sample Size

The initial sample size of 45 patients was based on the assumption that a sample size of 15 subjects per treatment group provided 90% power to detect an 8 milliliter (mL) difference between treatment groups in LV ESV, as measured by MRI, assuming a standard deviation of 6.5 mL.

A revised estimate of the standard deviation, based on a review of blinded LV ESV data from the first 11 subjects who completed treatment, suggests it may ultimately be as high as 9.4 mL. Accordingly, the sample size is being increased to around 22 subjects per treatment group, which provides 80% power to detect the aforementioned 8 mL difference between treatment groups. If necessary, the standard deviation will be reassessed in blinded fashion and the sample size modified accordingly.

11.2. Statistical and Analytical Plans

11.2.1. General Considerations

All study data are to be displayed in the data listings.

Statistical analysis of this study will be the responsibility of the Sponsor or its designee.

Additional details regarding analyses will be included in separate statistical analysis plan (SAP).

11.2.2. Subject Disposition

All subjects who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

11.2.3. Subject Characteristics

Subject's age, sex, weight, height, body mass index (BMI), and other demographic characteristics will be recorded and summarized by treatment group.

Relevant medical history will be listed.

11.2.4. Endpoints and Methodology

11.2.4.1. General Considerations

Data will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minima, and maxima) for continuous variables and using frequencies and percentages for discrete variables. Data will be presented by treatment group, as appropriate. Each active dose will be tested against placebo. Formal statistical tests (where performed) will be 2-sided and tested at the alpha=0.05 level of significance.

11.2.4.2. Analysis Populations

Approximately 70 adult subjects (age ≥40 and ≤80 years) will be randomized and will receive elamipretide or placebo according to the randomly assigned treatment sequence.

Statistical analysis will be performed in the following populations:

Per-Protocol Population – Includes subjects who meet minimal eligibility criteria, have sufficient information to determine the subject's outcome, and have no confounding factors that interfere with the assessment of that outcome. The Per-Protocol Population is further defined in the SAP.

Safety Population – Includes all study subjects who receive any amount of study medication according to treatment received.

Below only an outline of the data analyses are given. The details of all analyses will be described in the Statistical Analysis Plan to be finalized before unblinding.

11.2.5. Efficacy Analyses

For primary and secondary efficacy endpoints, the change from baseline in all continuous endpoints will be summarized using descriptive statistics (mean, median, standard deviation, minimum, maximum) by treatment group. Categorical variables will be described using frequencies and percentages by treatment group.

Efficacy analyses will be conducted on the Per-Protocol population. All test of treatment effects will be conducted at a 2-sided alpha level of 0.05.

Additionally, change in LV ESV measurements of all three treatment groups together will be analyzed by mixed model repeated measures (MMRM), in order to study trends in the treatment effects over 4 weeks, with the primary time point of interest being at Week 4. Additional details of the model, as well as adjustments for multiplicity (if needed) will be specified in the Statistical Analysis Plan.

Secondary and exploratory endpoints will be analyzed analogously.

11.2.6. Safety Analyses

Safety data analysis will be conducted on all subjects in the Safety Population.

11.2.6.1. Adverse Events

The number and percentage of subjects experiencing 1 or more AEs will be summarized by treatment group, relationship to study medication, and severity. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology. AEs will be summarized by system organ class (SOC), preferred term (PT), and treatment group.

All reported AEs will be listed, but only treatment-emergent adverse events (TEAEs) will be summarized.

The incidence of all TEAEs, drug relationship with TEAEs, and severity of TEAE will be summarized. In the summary tables, subjects may be counted under multiple SOCs and PTs, but for each SOC and PT, subjects are only counted once. If a subject has the same AE on multiple occasions, the highest severity (severe > moderate > mild) or drug relationship (probable > possibly related > unlikely related > unrelated) recorded for the event will be presented. If

severity is missing, subjects will be included as missing (for severity). If drug relationship is missing, subjects will be included in related tables (e.g., considered related).

11.2.6.2. Deaths and Other Serious Adverse Events

Listings will be provided for the following:

- Deaths
- SAEs
- SUSARs
- AEs leading to discontinuation of study medication

11.2.6.3. Clinical Laboratory Evaluations

Summary tables for laboratory parameters (including hematology, chemistry, and urinalysis) will include descriptive statistics of change relative to baseline where appropriate, and data listings of clinically significant abnormalities.

Subjects with laboratory data outside the normal range will be listed with abnormal values flagged.

Shift tables (e.g., tables that show the number of subjects who are low, normal, or high at baseline versus each post-baseline scheduled assessments) will be produced.

The number and percentage of subjects with urinalysis results outside the normal range will be presented by endpoint and visit for each treatment group. Shift tables for urinalysis will show the number of subjects who are normal/abnormal at baseline and normal/abnormal at the end of study.

11.2.6.4. Vital Signs

Vital signs data will be summarized by changes from baseline values at each treatment group using descriptive statistics.

Shift tables for heart rate and blood pressure (e.g., tables that show the number of subjects who are low, normal, or high at baseline versus each post-baseline scheduled assessment) will be produced.

11.2.6.5. Electrocardiogram

ECG data will be summarized by changes from baseline values at each treatment group using descriptive statistics.

Electrocardiogram results (normal versus abnormal) and an assessment of the clinical significance of any abnormalities (in the opinion of the Investigator) will be listed for individual subjects. Intervals of PR, QRS, QT, and QTc will also be listed.

11.2.6.6. Other Safety Parameters

Any other safety data captured on the eCRF will be listed.

12. INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

12.1. Informed Consent

The Investigator is responsible for ensuring that the subject understands the potential risks and benefits of participating in the study, including answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject willingness to continue his or her participation in the study.

The ICF will be used to explain the potential risks and benefits of study participation to the subject in simple terms before the subject is entered into the study, and to document that the subject is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The Investigator is responsible for ensuring that informed consent is given by each subject or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.

As used in this protocol, the term "informed consent" includes all consent and assent given by subject or their legal representatives.

12.2. Ethical Review

The Sponsor or its representatives must approve all ICFs before they are used at investigative sites. All ICFs must be compliant with the ICH guideline on GCP.

Documentation of EC approval of the protocol and the ICF must be provided to the Sponsor before the study may begin at the investigative site. The EC will review the protocol as required.

The study site's EC should be provided with the following:

- The current IB and updates during the course of the study
- ICF
- Relevant curricula vitae

12.3. Regulatory Considerations

This study will be conducted in accordance with:

1) Consensus ethics principles derived from international ethics guidelines, including the CIOMS International Ethical Guidelines
2) The ICH GCP Guideline [E6]
3) Applicable laws and regulations

The Investigator or designee will promptly submit the protocol to applicable EC(s). Some of the obligations of the Sponsor may be assigned to a third party organization.

An identification code assigned to each subject will be used in lieu of the subject's name to protect the subject's identity when reporting AEs and/or other study-related data.

12.3.1. Protocol Approval

The Sponsor's responsible medical officer will approve the protocol, confirming that, to the best of their knowledge, the protocol accurately describes the planned design and conduct of the study.

12.3.2. Final Report Approval

The Sponsor's responsible medical officer will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

12.3.3. Study Monitoring

The Investigators and institution(s) will permit study-related monitoring of the CRF data by Stealth BioTherapeutics Inc., or their assignee by providing direct access to source data and/or documents. The study monitor will verify the eCRFs against the source documentation. Deviations from the protocol with regard to subject enrollment or study conduct will also be noted in the source documentation, in the eCRF and a complementary database. A Sponsor representative will visit the site to initiate the study, prior to the first treatment of the first subject, and at agreed times throughout the study, including at the end of the study. Medication dispensing and clinical drug supply records will be verified at the study site by the study monitor. It is understood that all subject specific information is confidential and no documentation that can link study information to the specific subject will be collected or retained by the Sponsor.

12.3.4. Retention of Records

All study related material including source documents, eCRFs, Central Authority, and EC correspondence and analyses and any other documentation required by applicable laws and regulations will be maintained for 15 years after completion of the study or notification from the Sponsor that the data can be destroyed, whichever comes first.

12.3.5. Disclosure of Information

Information concerning the investigational medication and patent application processes, scientific data or other pertinent information is confidential and remains the property of Stealth BioTherapeutics Inc. The Investigator may use this information for the purposes of the study only. It is understood by the Investigator that Stealth BioTherapeutics Inc., will use information developed in this clinical study in connection with the development of the investigational medication and therefore may disclose it as required to other clinical Investigators and to regulatory agencies. In order to allow the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

The Investigator may not submit for publication or presentation the results of this study without first receiving written authorization from Stealth BioTherapeutics Inc. Stealth BioTherapeutics

Inc., agrees that before it publishes any results of the study, it shall provide the Investigator with at least 30 days for review of the pre-publication manuscript prior to the submission of the manuscript to the publisher.

13. REFERENCES

1. Mosterd A. et al., Clinical epidemiology of heart failure. Heart 2007; 93: p. 1137-1146.

2. Cook C. et al, The annual global economic burden of heart failure. Int J Cardiol 2014; 171(3): p. 368-76.

3. Shah A.M. et al., In search of new therapeutic targets and strategies for heart failure: recent advances in basic science. Lancet 2011; 378 (9792): p. 704-712.

4. McMurray J.J., Clinical practice. Systolic heart failure. N Engl J Med 2010; 362 (3): p. 228-238.

5. Hunt S.A. et al., 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009; 119 (14): p. e391-e479.

14. ATTACHMENTS

Attachment 1 Schedule of Assessments

	Screening Period	Treatment Period				Follow-Up Period
	Days -28 to -1 (Screening Visit)	**Day 1[a] (Baseline)**	**Week 1 (Day 8 + 3)**	**Week 2 (Day 15 ± 3)**	**Week 4/ED[b] (Day 29 + 3)**	**Week 6 (Day 43 ± 3)**
Informed Consent	X					
Demographics	X					
Randomization		X				
Review of Inclusion/Exclusion Criteria	X	X				
Relevant Medical History[c]	X	X				
Concomitant Medication Review	X	X	X	X	X	X
Review AEs		X	X	X	X	X
Cardiovascular Physical Examination[d]	X	X	X	X	X	X
Vital Signs[e]	X	X	X	X	X	X
12-Lead ECG	X	X	X	X	X	X
Blood Chemistry & Hematology	X	X	X	X	X	X
PK Samples[f]		X	X	X	X	X
Urinalysis	X	X			X	
Pregnancy Test[g]	X	X			X	
Echocardiography[h]	X	X			X	X
Cardiac MRI[i]	X		X		X	
KCCQ		X			X	
NT-pro-BNP		X	X	X	X	X
6-Minute Walk Test		X			X	
Borg dyspnea scale		X			X	
Study Medication Dispensing		X	X	X		
Study Medication Injection[j]		X----------X				
ISR Self-Assessment Questionnaire		X----------X				
Visiting Nurse/Investigator ISR Assessment[k]		X----------X				

[a] All Day 1 assessments should be performed prior to administering the first dose of study medication except the ISR assessments (as described in Section 6.3.9) and blood drawn for plasma analysis of elamipretide and metabolites (45 minutes post-injection ±15 minutes) (as described in Section 6.3.8.5) which should be completed after study medication administration.

[b] If a subject discontinues study medication early, the subject will have an Early Discontinuation Visit and will be asked to complete the Week 4 assessments.

[c] At the Screening Visit, a relevant medical history will be taken. Relevant medical history will be updated at the Day 1 visit.

[d] Cardiovascular physical examination including lung auscultation and weight. Height will only be measured at the Screening Visit.

[e] Vital signs measurements will include temperature, heart rate, respiration rate and blood pressure, recorded in the sitting position after at least 10 minutes rest.

[f] Blood samples for PK determinations of elamipretide and metabolites concentrations will be collected before administration of study medication and at 45 minutes (±15 minutes) post-dose at the Day 1, Week 1, and Week 2 visits, and at any time point at the Week 4 and 6 visit.

[g] Serum pregnancy test will be done for women of childbearing potential at the Screening visit. Urine pregnancy test will be done for women of childbearing potential on Day 1 and Week 4. The results of the Day 1 pre-dose pregnancy test must be evaluated before randomization to ensure eligibility.

[h] At the Screening Visit, only a 2-D echocardiography will be performed and it will be performed prior to Step 2 (blood draw, urinalysis) and Step 3 (cardiac MRI) screening procedures. Both 2-D and 3-D echocardiography will be performed at the Day 1, Week 4 and Week 6 visits.

[i] At the Screening visit, subjects will undergo delayed gadolinium-enhanced cardiac MRI prior to study medication injection. At the Week 1 visit, subjects will undergo cardiac MRI approximately 1 to 6 hours following injection of study medication.

[j] At Day 1, study medication injection will occur after the completion of baseline procedures (as noted in footnote a). Study medication will be administered daily by a Visiting Nurse, except on Study Visits, at Days 1 through 3 and during the Week 1 and Week 2 visits. The last dose of study medication will be administered on the day prior to the Week 4 visit.

[k] At each home visit, the Visiting Nurse will assess the current day's injection site. At Days 1 through 3, Week 1 and Week 2 visits, the Investigator (or designee) will assess the current day's injection site. The assessment will evaluate erythema, pain, swelling, and pruritus at the injection site at approximately 15 minutes post-injection. If any reaction is apparent, the injection site will also be evaluated at 30 minutes post-injection.

Attachment 2 Clinical Laboratory Tests

Hematology:	**Clinical Chemistry:**
Hemoglobin	**Serum:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Leukocytes (WBC)	Total bilirubin
Neutrophils, segmented	Alkaline phosphatase
Lymphocytes	Alanine aminotransferase (ALT)
Monocytes	Aspartate aminotransferase (AST)
Eosinophils	Blood urea nitrogen (BUN)
Basophils	Creatinine
Platelets	Calcium
	Glucose (non-fasting)
Urinalysis:	Albumin
Specific gravity	Chloride
pH	Bicarbonate
Protein	Total protein
Glucose	Triglycerides
Ketones	eGFR calculated with the MDRD study equation
Blood	hsTroponin I
Sodium	
Chloride	**Exploratory HF Biomarker**
Creatinine	NT-pro-BNP
Microalbuminuria	

Attachment 3 Six Minute Walk Test

Key Considerations:

- Consistency in administering the test is very important
- At least 30 minutes rest should be allowed between successive tests if applicable.
- If two successive tests are conducted results of both tests are recorded with the best result used to determine functionality.
- A health professional trained in CPR with the ability to run the test must be present or immediately available during the conduct of the 6MWT.

Required Equipment:

- Walking Track or Area - The walking track or area must be the same for all tests and all patients
    - The track may be a continuous track (oval or rectangular) or a point-to-point area (stop- turn around-go back).
    - Turns in the walking course should be minimized when possible
    - The track or area should be flat with no blind turns, traffic or obstacles.
    - The walking length should be 98.4 ft. (30m) and should be marked in 3 foot or 1 meter increments.
- Stethoscope, vital sign equipment, pulse oximeter
- Stop watch
- Portable oxygen delivery system
- Chairs at the starting position and along the walking course for the patient to rest if needed

Before the 6MWT:

- Confirm the patient has signed the ICF and the Principal Investigator has approved the subject's participation in the 6MWT.
- Instruct the patient to dress comfortably, wear appropriate footwear and to avoid eating for at least two hours before the test (where possible or appropriate).
- Any prescribed inhaled bronchodilator medication should be taken within one hour of testing or when the patient arrives for testing. All medications must be recorded as specified in the protocol.
- The patient should rest comfortably for at least 15 minutes before beginning the test.
- A comfortable ambient temperature and humidity should be maintained for all tests.
- Record:
    - Blood pressure
    - Heart rate
    - Respiratory rate
    - Oxygen saturation

Instructions to the Patient:

The instructions should be placed on a laminated card and read out loud to the patient. Instructions should be clear and consistent for every test conducted.

- Describe the walking track or area to the patient.
- Explain the objective of the test.
- Provide instructions on what to do and what not to do during the test.
- Emphasize the need for the patient to report any untoward effects.

Sample instructions:
"You are now going to do a six-minute walking test. The object of this test is to walk as quickly as you can for six minutes around the track (or up and down the corridor etc… depending on the track set up) so that you cover as much ground as possible. You may slow down if necessary. If you stop, I want you to continue to walk again as soon as possible. You will be kept informed of the time and you will be encouraged to do your best. Your goal is to walk as far as possible in six minutes. Please do not talk during the test unless you have a problem or if I ask you a question. You must let me know if you have any chest pain or dizziness. When the six minutes is up I will ask you to stop where you are. Do you have any questions?"

Begin the Test by instructing the patient to start walking and start the stop watch.

During the Test:

- Monitor the patient for untoward signs and symptoms.
- Use standard encouragements during the test.
    - At minute one: "Five minutes remaining. Do your best!"
    - At minute two: "Four minutes remaining. You're doing well - keep it up!"
    - At minute three: "Half way point. Three minutes remaining. Do your best!"
    - At minute four: "Two minutes remaining. You're doing well - keep it up!"
    - At minute five: "One minute remaining. Do your best!"

At the End of the 6MWT:

- Put a marker on the distance walked and record the value.
- Have the patient sit down or if the patient prefers, allow the patient to stand.

*Note: The measurements taken before and after the test should be taken with the patient in the same position.

- Immediately record oxygen saturation (SpO_2%), heart rate, and blood pressure on the recording sheet.
- Record respiratory rate
- Measure the distance remaining on the walking course with a tape measure and add up the total distance.
- The patient should remain in a clinical area for at least 15 minutes following an uncomplicated test.

Clinical Notes:
Normally the clinician does not walk with the patient during the test to avoid the problem of setting the walking pace. The pulse oximeter should be applied immediately if the patient chooses to rest and at completion of the six-minute walking period. Any delay may result in readings being recorded that are not representative of maximum exercise response.

In some instances, the clinician may choose to walk with the patient for the entire test (e.g., if continuous oximetry is desired). If this is the case the clinician should try to walk slightly behind the patient to avoid setting the walking pace. Alternatively, if the oximeter is small and lightweight, it may be attached to the patient and checked throughout the test without interfering with walking pace.

If the Patient Stops During the Six Minutes:

- Allow the patient to sit in a chair if they wish.
- Measure the SpO_2% and heart rate.

- Ask the patient why they stopped and record the reason stated.
- Record the time the patient stopped (but keep the stop watch running).
- Encourage the patient to begin walking as soon as he/she is feeling better and offer encouragement every 15 seconds if necessary.
- Monitor the patient for untoward signs and symptoms.

Stop the Test in the Event of Any of the Following:

- Chest pain suspicious for angina.
- Evolving mental confusion or lack of coordination.
- Evolving light-headedness.
- Intolerable dyspnea.
- Leg cramps or extreme leg muscle fatigue.
- Persistent $SpO_2 < 85\%$.
- Any other clinically warranted reason.

References:

ATS Statement: Guidelines for the 6MWT Am J Respir Crit Care Med 2002; 166: 111-117.

Olsson et al Eur Heart Journal 2005; 26: 778-793.

Miyamoto et al Am J Respir Care 2000; 161: 487-492.

Attachment 4 Kansas City Cardiomyopathy Questionnaire (KCCQ)

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 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** bothersome	**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** bothersome	**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 . . .

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**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
□	□	□	□	□

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

	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	□	□	□	□	□	□

Attachment 5 Injection Site Reaction (ISR) Self-Assessment Questionnaire[a]

Please answer each question below by checking the box that best represents your opinion (Check only one box per question). Select "Not at all" if you did not experience the injection site reaction.

1. During and/or after the injection of today's dose of study medication, how **bothered were you** by the following potential pain and skin reactions at the injection site:

	Not at all	A little	Moderately	Very	Extremely
a. pain?	☐	☐	☐	☐	☐
b. burning sensation?	☐	☐	☐	☐	☐
c. cold sensation?	☐	☐	☐	☐	☐
d. itching?	☐	☐	☐	☐	☐
e. redness?	☐	☐	☐	☐	☐
f. swelling?	☐	☐	☐	☐	☐
g. bruising?	☐	☐	☐	☐	☐

[a] Adapted from the Self-Injection Assessment Questionnaire © 2011 Keininger and Coteur; licensee BioMed Central Ltd.

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE

Attachment 6 Table for Grading the Severity of Site Reactions to Injections and Infusions (Adults)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling	Same as for **Injection Site Erythema or Redness**	Same as for **Injection Site Erythema or Redness**	Same as for **Injection Site Erythema or Redness**	Same as for **Injection Site Erythema or Redness**
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

Adapted from Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2, November 2014.

Attachment 7 Modified Borg Dyspnoea Scale

Subject Instructions for Modified Borg Dyspnoea Scale

"This is a scale that asks you to rate the difficulty of your breathing, in this case after you have lain flat for up to ten minutes – or if you cannot manage that how breathless you imagine you would be if you tried to lie flat.

It starts at number 0 where your breathing is causing you no difficulty at all and progresses through to number 10 where your breathing difficulty is maximal. How much difficulty is your breathing causing you right now?"

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal