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DEVELOPING ORAL LT3 THERAPY FOR HEART FAILURE (DOT$_3$HF)

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List of Abbreviations

AE	adverse event
BNP	B-type natriuretic peptide
CHPS	Center for Human Phenomic Science
CVD	cardiovascular disease
CRT	cardiac resynchronization therapy
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
FDA	Food and Drug Administration
FT4	free thyroxine
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HUP	Hospital of the University of Pennsylvania
ICD	implantable cardioverter-defibrillator
IDS	Investigational Drug Services Pharmacy
IRB	Institutional Review Board
IV	intravenous
KCCQ	Kansas City Quality of Life Questionnaire
LT3	liothyronine
LV	left ventricular
NIH	National Institutes of Health
NHLBI	National Heart Lung and Blood Institute
NT-pro-BNP	N-terminal pro hormone B-type natriuretic peptide
PHI	protected health information
REE	resting energy expenditure
SD	standard deviation
ThyPRO	Thyroid-specific Patient Reported Outcome Measure
T3	triiodothyronine
T4	thyroxine
TSH	thyroid stimulating hormone

Study Summary

Title	**DEVELOPING ORAL LT3 THERAPY FOR HEART FAILURE (DOT3HF)**
Short Title	**Developing Oral LT3 Therapy for Heart Failure**
IRB Number	**833681**
Phase	Phase I/II
Methodology	Parallel, Randomized, Double-Blind, Placebo-Controlled Crossover Clinical Trial
Study Duration	48 Months
Study Center(s)	Single-Center: University of Pennsylvania Health System
Objectives	The primary objective is to evaluate the safety of oral LT3 in heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) The secondary objective is to evaluate the feasibility and preliminary efficacy outcomes of oral LT3 therapy in HFrEF and HFpEF.
Number of Participants	28 in HFrEF arm and 28 in HFpEF arm, totaling 56 randomized participants
Main Inclusion and Exclusion Criteria	**Inclusion:** ≥18 years; NYHA Class I,II or III heart failure; normal TSH and free T4 levels; Total T3 level <94 ng/dL

- **HFrEF inclusion** - Left ventricular (LV) ejection fraction (EF)≤40 percent, an implantable cardioverter-defibrillator (ICD), on stable doses of neurohormonal blockade for 30 days

HFpEF inclusion - dyspnea on exertion and/or clinical evidence of heart failure by history and physical examination, LV EF≥40 percent, If taking antihypertensive medications, beta-blockers, SGLT2 inhibitors, sacubitril/valsartan, or aldosterone antagonists, doses must be stable for at least 30 days and elevated filling pressures as evidenced by at least 1 of the following:

1. Mitral E/e' ratio > 14 (either lateral or septal)
2. Mitral E/e' ratio > 8 (either lateral or septal), with low e' velocity (septal e'<7 cm/sec or lateral e'< 10 cm/sec), in addition to one of the following:
   a. Enlarged left atrium (LA volume index >34 ml/m^2)
   b. Chronic loop diuretic use for control of symptoms
   c. Elevated natriuretic peptides (BNP levels >100 ng/L or NT-proBNP levels >300 ng/L)
   d. Tricuspid regurgitation velocity >2.8 m/s
3. Elevated invasively-determined filling pressures previously (resting LVEDP >16 mmHg or mean pulmonary capillary wedge pressure [PCWP] >12 mmHg; or PCWP/LVEDP ≥25 mmHg with exercise)
4. Acute heart failure decompensation with radiographic evidence of pulmonary venous congestion or alveolar edema, requiring IV diuretics within the past year
5. Probability of HFpEF>90% according to the HFpEF score, without a more likely clinically apparent cause for symptoms, as per investigator assessment

Exclusion: Hypertrophic or restrictive cardiomyopathy; uncorrected severe primary valvular disease;; inability to perform VO2max exercise testing; severe lung disease; serum creatinine > 3.0 mg/dL; history of cirrhosis; acute coronary syndrome or coronary artery intervention or ablation therapy within past 2 months; cardiac surgery, percutaneous repair of a valve or septal defect, or initiation of cardiac resynchronization therapy within the past 6 months; chronic intravenous inotrope therapy; ventricular assist device therapy; heart failure hospitalization within past month; taking thyroid extract, LT4, LT3, amiodarone, or medication that affects the absorption or metabolism of thyroid hormone; gastrointestinal conditions that affect the absorption of thyroid hormone; current or planned pregnancy within the timeframe of study participation.

Investigational Product (drug, biologic, device, etc.)

Oral Liothyronine, 5 mcg tablet, dose range from 2.5 mcg three times a day to 12.5 mcg three times a day

For Drug, food, cosmetic, etc. include the dose,

route of administration and dose regimen	
Duration of administration (if applicable)	Eight Weeks
Reference therapy	Placebo
Statistical Methodology	Safety data will be monitored and reported by descriptive statistics where applicable. Rhythm monitoring will be described using measures of central tendency and variation, as well as frequencies and percentages. Frequencies and percentages will be used to describe participants with T3 levels above the upper limit of reference range (180 ng/dL) at the completion of each drug.
Safety Evaluations	Safety evaluations will be the frequency of safety events while on placebo compared to while on LT3, T3 levels, and rhythm monitoring.
Data and Safety Monitoring Plan	All safety events will be assessed in real time and at study completion by the PI's. This study will also have a DSMB in place to review participant safety data and study conduct and progress (biannually or at DSMB determined frequency). In addition, an internal study monitor will provide study oversight biannually.

Introduction

This study will be conducted in full accordance all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations including [as applicable include the following regulations as they apply 45 CFR 46, 21 CFR Parts 50, 54, 56, 312, 314 and 812 and Good Clinical Practice].

1 Background and Study Rationale

1.1 Background and Relevant Literature

Heart failure is the most common reason for adult hospitalization in the developed world.[1,2] Many patients with heart failure have low levels of the thyroid hormone triiodothyronine (T3). Therapies that target reversible causes of myocardial and peripheral organ dysfunction are likely to provide added benefit in heart failure with reduced ejection fraction (HFrEF). In addition, there are no proven effective pharmacologic therapies for heart failure with preserved ejection fraction (HFpEF), which accounts for ≥50% of the heart failure burden.[3]

Triiodothyronine (T3), an endogenous thyroid hormone, exerts multiple effects on the cardiovascular system, mediated through T3 receptors in the myocardium and vasculature and directly on ion channels and mitochondria.[4] Overarching effects of T3 include an increase in myocardial contractility and a decrease in systemic vascular resistance. Despite the high prevalence (~20-30%) of low T3 syndrome in heart failure,[5,6] the exogenous administration of liothyronine (LT3), the synthetic form of T3, remains an underexplored therapeutic option. Approximately 20% of circulating T3 is produced directly from the thyroid, whereas the remaining 80% is produced from the conversion of circulating thyroxine (T4) to T3.

Low T3 syndrome has been associated with increased mortality in patients with HFrEF[6-8] and disease severity in HFpEF[9], but whether it is a marker of poor health or a mediator of clinically relevant abnormalities in heart failure is unknown. The overall goal of this study is to determine the safety, feasibility, and preliminary efficacy of oral LT3 therapy in patients with Heart Failure (HF) and low T3.

Proof of concept clinical studies using short-term intravenous LT3 infusions have demonstrated beneficial effects on biomarkers and safety in patients with ischemic HFrEF. However, knowledge gaps remain regarding the safety of oral LT3 therapy in HFrEF. Furthermore, no studies have examined LT3 safety in HFpEF.

Low T3 is highly prevalent and predicts poor prognosis in patients with heart failure.
Thyroid dysfunction is implicated as a poor prognostic factor in heart disease. The low T3 syndrome, defined as a low T3 level with levels of TSH and free T4 within the normal reference range, is present in 20-30% of patients with HFrEF.[5,6] The hypothesized mechanism of low T3 is through increased cytokine levels and hypoxia, which lead to decreased conversion of T4 to T3 and increased clearance of T4 to reverse T3.[4] Low serum T3 levels are associated with myocardial fibrosis and abnormalities in myocardial perfusion and metabolism in patients with idiopathic dilated cardiomyopathy.[7] In studies of hospitalized patients with heart failure, low T3 syndrome was independently associated with higher all-cause mortality.[6,8,9] These data have recently been extended to outpatients with chronic heart failure.[10]

Although less is known about the effects of low T3 in HFpEF, data from one cross-sectional study

of 89 patients with HFpEF found that 22% had low T3 syndrome.[11] In addition, T3 levels below the median were associated with higher levels of BNP and greater severity of diastolic dysfunction. Our unpublished data show a 29% prevalence of low T3 syndrome in patients with HFpEF and associations of low T3 with worse cardiac function.

LT3 has been available for over 60 years but has not been studied for this indication. Establishment of benefit/dosing and acceptable safety of LT3 therapy in patients with HFrEF and/or HFpEF is needed. In addition, feasibility and preliminary efficacy data produced could be used to design trials to test whether LT3 therapy, when dosed appropriately, can benefit patients with HF, definitively answering the question of whether or not to pursue larger studies of LT3 administration in HF.

HFrEF treatment rationale

There are opportunities for improvement in treatment of HFrEF. Current approaches to treatment of chronic HFrEF include device therapies that support myocardial function and pharmacotherapies that counteract the neurohormonal response to the failing heart. ICDs also improve outcomes by aborting sudden death from ventricular arrhythmia. Improved survival has been shown with cardiac resynchronization therapy (CRT), which has a direct effect on the myocardium, and with beta blockers, angiotensin-converting-enzyme inhibitors, angiotensin receptor-neprilysin inhibitors, hydralazine plus nitrate, and aldosterone antagonists, which curb the neurohormonal response. Certain therapies appear to have greater benefit in specific subpopulations of patients with HFrEF, such as hydralazine plus nitrates in blacks[12] or ivabradine in patients with resting heart rate ≥70 beats per minute.[13]

Despite the therapeutic success of CRT, previously developed drugs targeting ventricular function have had mixed experience. Potent oral and intravenous inotropes, which augment β1-adrenergic signaling through cAMP, acutely improve hemodynamics and symptoms in advanced disease, but have failed to show survival benefit and may be harmful with chronic administration, though such data were collected largely in the pre-ICD era.[14-16] In contrast, milder inotropic agents, such as digoxin, lower the risk of heart failure readmission and may favorably affect survival in patients with therapeutic digoxin levels.[17,18] An important lesson is that a precise understanding of the pharmacologic effects and dose-response in the cardiovascular system are essential steps in assessing therapeutic potential. Thyroid hormone is a key endogenous regulator of cardiac function and its effects require precise regulation: cardiac effects occur from thyroid hormone excess as well as deficiency. T3 deficiency is highly prevalent in HFrEF, but the therapeutic potential of correcting T3 levels in HFrEF has not been explored.

HFpEF treatment rationale

There is an urgent need to identify effective agents for the treatment of chronic HFpEF. Approximately half of HF is secondary to HFpEF, which is anticipated to represent an even larger proportion of the total burden of HF as the population ages.[19] In contrast to chronic HFrEF, there is a pronounced paucity of effective interventions in chronic HFpEF, and no proven effective pharmacologic intervention to improve outcomes in this condition. Multiple phase 3 trials over the last few decades have failed to demonstrate a clear benefit of various pharmacologic interventions. Recent therapeutic successes have occurred in HFpEF, due to the appreciation of the importance of well-conducted early phase trials that characterize the mechanisms and dose-response of specific interventions.[20-28] Detailed hemodynamic and cardiac phenotyping has provided important insights into the pathophysiology of LV remodeling and fibrosis, diastolic dysfunction, microvascular disease, and impaired oxygen delivery to peripheral skeletal muscle, all of which contribute to exercise intolerance, the cardinal feature of HFpEF.[3] Furthermore, heterogeneity in the underlying processes that contribute to HFpEF is increasingly recognized.

The ability to identify individuals with a specific abnormality (low T3) that can be targeted by a pharmacologic intervention represents a promising approach.[29]

1.2 Interventional Agent: Liothyronine (L-triiodothyronine or LT3)

Liothyronine (L-triiodothyronine or LT3) is the synthetic form of the natural thyroid hormone triiodothyronine (T3), available as the sodium salt. LT3 is most often used to treat hypothyroidism and has been used for over 60 years. Liothyronine is the active form of thyroxine, which is composed chemically of tyrosine with bound iodine. The half-life of LT3 is one to two days.[30]

1.2.1 Nonclinical Data

Preclinical studies support beneficial effects of T3 on myocardial contractility, myocardial relaxation, and vascular resistance. Molecular studies have elucidated the effects of T3 in cardiac myocytes. T3 enters the cardiomyocyte through membrane transporters, or it is produced intracellularly from conversion of T4 to T3 by type 2 deiodinase. T3 binds to nuclear receptors bound to thyroid hormone response elements present in the regulatory regions of target genes, acting to regulate the expression of a number of genes that encode key proteins including α and β myosin heavy chain, Na^+K^+ ATPase, sarcoplasmic reticulum Ca^{2+} ATPase, and phospholamban.[4] Nongenomic effects of T3 are mediated through alterations in ion flux through ion channels such as the sarcolemmal Na^+ channel, inward-rectifying K^+ channel, and voltage-activated potassium channels.[31] Together, these cellular actions contribute to the inotropic and lusitropic effects of T3.

Since intracardiac deiodination of T4 to T3 occurs, it would seem that as long as there were sufficient circulating T4, intracardiac T3 would be preserved. However, two studies in thyroidectomized rats have shown that LT4 administration fails to restore intracardiac T3 levels.[32,33] In addition, in a rat model of HF due to ischemic cardiomyopathy, infusion of LT3 restored contractility to that of control animals.[34] This has led to the hypothesis that the failing heart is a hypothyroid heart due to intracellular T3 deficiency, irrespective of circulating T4 levels.[35]

1.2.2 Clinical Data to Date

1.2.2.1 Clinical Studies in Adults

Research in humans suggests safety of oral LT3 in patients without pre-existing cardiac disease.

In 1891, the use of thyroid extract, which was generated from ground sheep thyroid glands, was reported as the first successful treatment for hypothyroidism.[36] Subsequent research led to the isolation of T4 in 1914 as the major hormone produced by the thyroid gland, and to commercial synthesis of LT4 in 1927 as an alternative to thyroid extracts.[37] Since thyroid hormone medications were not new drugs, thyroid extracts and LT4 were exempt from the 1938 Food, Drug, and Cosmetic Act, which required that new drugs be tested for safety. They were permitted to remain on the market without testing. T3 was isolated from the thyroid gland and synthesized in 1954. Cytomel was the first LT3 medication to be approved in 1956. Thyroid medications were again grandfathered in after the 1962 overhaul of the Food, Drug, and Cosmetic Act, and their manufacturers never had to submit scientific data or get full FDA approval. Concerns among endocrinologists about adverse cardiac effects from high doses of LT3,[38] recognition that T4 is converted to T3 peripherally,[39] the longer half-life of LT4 compared to LT3, and aggressive marketing by the manufacturer of Synthroid led to dominance of LT4 thyroid hormone

replacement in the 1970's.

LT4 therapy remains the mainstay of treatment of hypothyroidism. LT3 is often added to a loading dose of LT4 in patients hospitalized with myxedema coma (5-20 mcg loading dose, followed by 2.5-10 mcg every 8 hours).[40] Despite its potential, use of LT3 therapy in other settings, such as in combination with LT4 therapy to treat hypothyroidism, is not currently recommended by the American Thyroid Association and European Thyroid Association guidelines for thyroid hormone replacement, due to a paucity of data from adequately designed studies.[40,41] Well-designed studies are needed to test LT3's potential clinical impact.

Overt hyperthyroidism (low TSH with elevated free T4 or T3) and subclinical hyperthyroidism (low TSH with normal free T4 and T3) are each associated with an increased risk of atrial fibrillation.[42-44] Excess T3 from high doses of thyroid extract has been associated with increased cardiac symptoms.[45] However, studies of combination LT4-LT3 therapy performed in over 1400 patients studied for 5 weeks to 12 months have not shown any increase in cardiac symptoms or events in patients taking combination therapy compared with standard LT4 therapy,[40] nor has a small cross-over study of complete replacement of LT4 for LT3.[46] A Scottish registry study of 400 patients taking LT3 showed similar rates of atrial fibrillation and cardiovascular events to 33,955 patients taking LT4 therapy.[47] Thus, although conditions of thyroid hormone excess increase risk of atrial fibrillation, data from studies and clinical practice do not support any increased arrhythmic risk from LT3 administration. This study will have careful monitoring of T3 levels, target levels within the reference range to prevent thyroid hormone excess, cardiac monitoring to detect any arrhythmic signal, and for the patients with HFrEF, ICDs in place.

1.2.2.2 Proof of Concept Studies

Proof of concept clinical studies using short-term intravenous LT3 infusions have demonstrated safety and efficacy in patients with heart failure. Though preclinical studies support the role of LT3 therapy in heart failure, little is known about the optimal route, dose, and frequency of LT3 therapy in humans. Clinical studies using short-term intravenous infusions of LT3, lasting a few hours to 3 days, show acceptable safety in patients without pre-existing thyroid dysfunction undergoing coronary artery bypass surgery and in heart failure.[48-51] Hamilton *et al* administered a bolus followed by a 6 to 12 hour infusion of LT3 in 23 patients with HFrEF and showed increased cardiac output and decreased peripheral vascular resistance in 6 of 7 patients receiving the highest dose.[50] Pingitore *et al* performed a 3 day infusion of LT3 (n=10) or placebo (n=10) in patients with HFrEF and showed improvements in N-terminal pro-B-Type natriuretic peptide, noradrenaline, and aldosterone in the LT3 group, along with an improvement in stroke volume, without changes in external and intracardiac workload.[51] In both studies, LT3 was well tolerated without increased heart rate or arrhythmias. However, these studies were short-term, used intravenous LT3, and did not address HFpEF.

1.3 Dose Rationale (if applicable)

Only one study has evaluated the effects of oral LT3 therapy, at a mean dose of 20 mcg daily (range 10-40 mcg) for 3 months, in 13 individuals who had low T3 syndrome and HFrEF with very mild reductions in ejection fraction at baseline (LV EF =43%).[52] There was a non-statistically significant improvement in ejection fraction (43.3 vs. 46.0%; p=0.27) in this cross-over study, though it is arguable that ejection fraction was an appropriate primary endpoint for these patients. In addition, their twice daily dosing regimen and dependence on TSH levels instead of T3 levels for titration resulted in a small mean change in T3 levels (0.3 nmol/L; 20 ng/dL), which could have been insufficient to induce a meaningful physiologic effect. Cardiac monitoring for the first 48

hours did not detect any arrhythmias, and LT3 was well tolerated. A phase 2 study of the thyroid analog DITPA was halted early due to poor tolerance, despite improvements in cardiac index, systemic vascular resistance, cholesterol, and body weight.[53] It is possible that too high a dose was selected for this study and that a dose ¼ of that used would have been tolerated while still achieving efficacy.

These studies highlight the need for careful, individualized titration to stay within T3's therapeutic window.

We will be titrating LT3 to T3 levels, not TSH levels. The TSH level is a biomarker for pituitary sensitivity to T3, whereas the T3 assay is a direct measurement of circulating T3. At this time, there is no biomarker for cardiac tissue sensitivity to T3. The single published study of oral LT3 in HF titrated the LT3 dose to the TSH level, whereas the 3-day IV LT3 in HF study titrated LT3 dose to the T3 level.[51,52] The 24-hour dose in the oral LT3 study was 2/3 of the dose in the IV LT3 study; only the IV LT3 study demonstrated a clinically meaningful difference. We will measure total T3 levels from 2-4 hours after the LT3 dose, which represents the peak T3 level,[54,55] to ensure that T3 level remains within the reference range throughout the day. There is little diurnal variation of endogenous T3, with only an 11% difference between peak and nadir levels.[56] Endogenous peak T3 levels occur at approximately 4 am,[56] which will not coincide with the peak T3 level from our planned evening LT3 dose. Within-person assessments of T3 levels are stable when assessed daily[51] or monthly.[57] Although, in theory, the free T3 assay should be more biologically relevant than the total T3 assay, measurement of pg/mL quantities of free T3 can be challenging. As such we will measure total T3, as recommended by the American Thyroid Association.[58]

In this study, administration of liothyronine (LT3) will begin with an initial dose of 15 mcg daily. Dose titration of LT3 and matching placebo will be overseen by an unblinded study physician based on measured T3 levels. Pharmacokinetic data suggest that 5 mcg three times daily should not result in T3 excess in patients with low endogenous T3 levels.[54] The titration phase will be ~four weeks, followed by a ~four week maintenance phase, before crossover. There will be a ~weekly titration of active drug and matched titration of placebo over ~four weeks based upon peak total T3 levels obtained 2-4 hours after the morning LT3 dose. After ~four weeks of titration, the minimum LT3 dose will be 2.5 mcg three times daily (7.5mcg) and the maximum LT3 dose will be 12.5 mcg three times daily (37.5mcg), to be maintained for ~4 additional weeks. The ~2-week washout between intervention periods will be of sufficient duration to metabolize exogenous LT3 due to the short half-life of LT3, which is less than a day. The low initial dose described, gradual titration planned, and careful monitoring of T3 levels in addition to vigilant AE monitoring all will protect participants in relation to study dosing.

2 Study Objectives

Our overall goal is to determine the safety, feasibility, and preliminary efficacy of oral LT3 therapy in patients with HF and low T3. We will assess the safety and preliminary efficacy of administering oral LT3 therapy in the two independent study populations in parallel: HFrEF and HFpEF. It is anticipated LT3 will be well tolerated without T3 excess, and that treatment with LT3 will show no evidence of increased AEs or arrhythmic events compared to placebo. We anticipate that secondary endpoints will provide sufficient estimates of effect size and variability in HF populations to enable accurate power calculations for future phase 2 trials focused on efficacy of LT3.

2.1 Primary Objective

- To determine the safety of oral LT3 therapy in heart failure with low T3 syndrome

2.2 Secondary Objectives

- To determine the feasibility of oral LT3 therapy in heart failure with low T3 syndrome
- To determine the preliminary efficacy of oral LT3 therapy in heart failure with low T3 syndrome
- To determine the plausible mechanistic pathways of LT3 effect

3 Investigational Plan

3.1 General Design

The study is designed as two parallel randomized, double-blind, placebo-controlled cross-over studies with a ~2-week washout period between treatments (Figure 1). We will simultaneously investigate the safety, feasibility, and preliminary efficacy of thyroid hormone therapy (LT3) in individuals diagnosed with heart failure and low T3 syndrome: HFrEF individuals in one arm and HFpEF individuals in a second arm. Within each group, each treatment period will be ~8 weeks in duration, with ~weekly titration of study drug for ~four weeks, followed by a maintenance dose for ~4 weeks, then ~2-week washout before crossing over to the other arm. We will be titrating LT3 to T3 levels, measuring total T3 levels 2-4 hours after the LT3 dose.

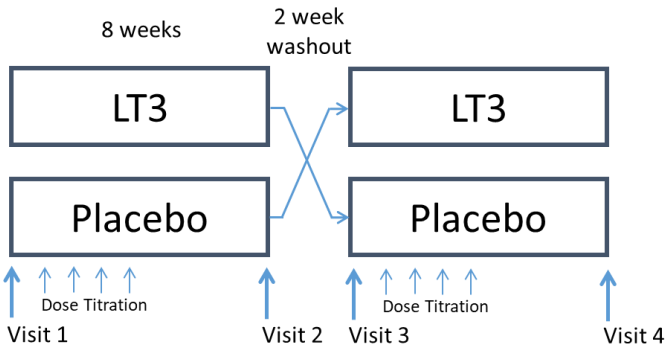

Figure 1. Study design

The study drug will be dispensed in person at Visits 1 and 3. A pill cutter will also be provided at Visit 1. LT3 will be dosed three times daily to maintain stable levels.[55] Liothyronine Sodium Tablets, USP in the 5 mcg dose and matching placebo tablets will be stored and dispensed from Penn's IDS.

The initial dose of LT3 started at Visit 1 will be 15 mcg (5 mcg three times daily: pre-breakfast, mid-afternoon, and bedtime). Six to nine days after initiation, the participant will go to a Penn-affiliated laboratory for a peak total T3 measurement 2-4 hours after the morning dose. The following day, the unblinded study physician will call the participant to recommend continuing this dose if the total T3 level is >160 but <180 ng/dL (the upper limit of the reference range) vs. titration to 22.5 mcg (7.5 mcg three times daily) if the total T3 level ≤ 160 ng/dL. Pharmacokinetic data suggest that 5 mcg three times daily should not result in T3 excess in patients with low endogenous T3 levels.[54] If the total T3 level is >180 ng/dL, the dose will be reduced to 7.5 mcg

(2.5 mcg three times daily), and the total T3 level will be rechecked the following week.

The process of T3 assessment ~6 days after a dose change or confirmation and dose titration on the ~7th day will continue for an additional 3 weeks, to a maximum dose of 12.5 mcg three times daily. A titration in the placebo group will occur in parallel to LT3 titration. The titration phase will be ~4 weeks in duration, followed by a ~4-week maintenance dose phase. After ~8 weeks, there will be a study assessment in the CHPS research unit (Visit 2). This will be followed by a ~two-week washout and another assessment (Visit 3). Participants will cross-over and receive the alternate therapy, following the same titration scheme as in the initial ~8-week period and will undergo assessment in CHPS unit at Visit 4. Some flexibility (up to 3-day delays for titration assessments and up to 3 days before or after due dates for the maintenance dose and washout phases) will be allowed in the timing of these visits due to weekend, holidays, CHPS services availability, and/or participants' personal circumstances.

The primary safety outcomes will be T3 levels within range and arrhythmias. Additional testing at study visits include peak VO2, quality of life, NT-proBNP level, physical activity, echocardiography, tonometry measurements, resting energy expenditure, weight, and hyperthyroid symptoms. The length of active participation for each participant who qualifies for entry in the study will be ~19 weeks with a follow up phone call 1 week after Visit 4.

3.1.1 Screening Phase

Potential participants will be recruited from the University of Pennsylvania Health System's three Philadelphia hospitals and affiliated outpatient practices. We will use a 2-stage written informed consent process. A study team coordinator will pre-screen focusing on identifying potential study participants in general cardiology clinics, heart failure/transplant clinics, internal medicine clinics, and the echocardiography laboratory. Potential participants who may fit criteria for enrollment based on record review will be consented for a screening TSH, free T4, and Total T3 blood test (See IRB # 833103 protocol/ICF for details). Additionally, data about medical history, medications, and social habits may be collected at this time. They will be provided with a brief overview of the study and will be informed that if they qualify, we will approach them for a more detailed discussion later. If they consent, the TSH, free T4, and total T3 will be obtained. If they are eligible based upon this information, they will be scheduled for a Visit 1.

3.1.2 Study Intervention Phase

At the baseline study visit (Visit 1), the participant will be randomized to LT3 or placebo. Dose titration of LT3 and matching placebo will be overseen by an unblinded study physician based on measured T3 levels. The initial dose of LT3 will be 15 mcg (5 mcg three times daily: pre-breakfast, mid-afternoon, and bedtime). At least six days (>6 half-lives of LT3) after initiation (range: 6-9 days), the participant will go to a Penn-affiliated laboratory for a peak total T3 measurement 2-4 hours after the morning dose. The following day, the unblinded study physician will call the participant to recommend continuing this dose if the total T3 level is >160 but <180 ng/dL (the upper limit of the reference range) vs. titration to 22.5 mcg (7.5 mcg three times daily) if the total T3 level ≤ 160 ng/dL. Pharmacokinetic data suggest that 5 mcg three times daily should not result in T3 excess in patients with low endogenous T3 levels. If the total T3 level is >180 ng/dL, the dose will be reduced to 7.5 mcg (2.5 mcg three times daily), and the total T3 level will be rechecked the following week.

The process of T3 assessment at least 6 days (range: 6-9 days) after a dose change or confirmation and dose titration on the 7th day will continue for an additional ~3 weeks, to a maximum dose of 12.5 mcg three times daily (37.5 mcg). A titration in a placebo participant will occur in parallel to each LT3 titration. The titration phase will be ~4 weeks in duration, followed by a ~4-week maintenance phase.

After ~8 weeks, there will be a final study assessment on therapy in the CHPS research unit (Visit 2). This will be followed by a ~two-week washout. Participants will have a repeat assessment at week 10 (Visit 3), cross-over, and receive the alternate therapy, following the identical titration scheme to the initial ~8-week period and a final assessment (Visit 4) at ~week 19.

3.1.3 *Follow Up Phase*

One week following Visit 4, a telephone follow-up call will be placed to assess for adverse events and answer any remaining participant questions regarding the study and intervention.

3.1.4 Allocation to Interventional Group

Study drug randomization and dispensing will be performed through the Penn Investigational Drug Service (IDS). A randomization list for the order of study drug administration (LT3 or placebo) will be created by the Investigational Drug Services (IDS) using a web-based program, separately for each arm (HFrEF and HFpEF). Compliance with the randomization schemes for each study will be maintained by IDS in dispensing individual participant medication throughout the study.

3.1.5 Primary Study Endpoints

The primary study endpoints will be safety endpoints: Total T3 concentrations within upper limit of reference range (180 ng/dL); EKG assessment of arrhythmic events; cardiac monitoring 14 day adhesive patch electrocardiographic monitoring of arrhythmic events; and for the HFrEF arm only, ICD interrogation of arrhythmic events.

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The assessments below are required for assessment of LT3 safety

- Total T3 concentrations within upper limit of reference range (180 ng/dL)
- EKG assessment of arrhythmic events:
- Cardiac Monitoring14 day adhesive patch electrocardiographic monitoring of arrhythmic events
- ICD interrogation of arrhythmic Interrogation will occur after study completion (HFrEF only)

3.1.6 Secondary Study Endpoints

The secondary study endpoints will be preliminary efficacy endpoints: Peak oxygen consumption during a maximal effort exercise test (peak VO2); Quality of life (Kansas City Cardiomyopathy Questionnaire, KCCQ); Remotely sensed physical activity (actigraphy); NT-proBNP levels.

The assessments below are clinically relevant efficacy outcomes:

- Peak oxygen consumption during a maximal effort exercise test (peak VO_2)
- Quality of life (Kansas City Cardiomyopathy Questionnaire, KCCQ
- Remotely sensed physical activity (actigraph)
- NT-proBNP levels

Mechanistic and Other secondary endpoints:

- LV function, arterial load, and ventricular-arterial interactions via simultaneous Doppler echocardiography and arterial tonometry
- Resting energy expenditure
- Weight: At Visits 1-4, weight will be measured in the CHPS unit using a calibrated scale.
- ThyPRO questionnaire section for hyperthyroid symptoms:
- Thyroid function tests: Serum will be drawn for TSH, free T4, total T3, and reverse T3

4 Study Population and Duration of Participation

4.1 Major Inclusion Criteria

HFrEF Inclusion

1. Men and women aged ≥18 years
2. NYHA Class I, II or III heart failure
3. EF≤40 percent within the past year
4. An implantable cardioverter-defibrillator (ICD)
5. Stable doses of neurohormonal blockade for 30 days
6. TSH of 0.27-5.33 mU/L and Free T4 level of 0.61-1.70 ng/dL and total T3 level <94 ng/dL
7. If taking oral estrogen, dose must remain stable for duration of study participation.

HFpEF Inclusion

1. Men and women aged ≥18 years
2. NYHA Class I, II or III heart failure or dyspnea on exertion without a clinically identifiable alternative cause
3. LV EF≥40 percent
4. If taking antihypertensive medications beta-blockers SGLT2 inhibitors, sacubitril/valsartan, or aldosterone antagonists, doses must be stable for at least 30 days
5. Elevated filling pressures as evidenced by at least 1 of the following:
    a. Mitral E/e' ratio > 14 (either lateral or septal)
    b. Mitral E/e' ratio > 8 (either lateral or septal), with low e' velocity (septal e'<7 cm/sec or lateral e'< 10 cm/sec), in addition to one of the following:
        i. Enlarged left atrium (LA volume index >34 ml/m^2)
        ii. Chronic loop diuretic use for control of symptoms
        iii. Elevated natriuretic peptides (BNP levels >100 ng/L or NT-proBNP levels >300 ng/L)
        iv. Tricuspid regurgitation velocity >2.8 m/s
    c. Elevated invasively-determined filling pressures previously (resting LVEDP>16 mmHg or mean pulmonary capillary wedge pressure [PCWP] > 12 mmHg; or PCWP/LVEDP≥25 mmHg with exercise).
    d. Acute heart failure decompensation requiring IV diuretics within the past year
    e. Probability of HFpEF>90% according to the HFpEF score, without a more likely clinically apparent cause for symptoms, as per investigator assessment
6. TSH of 0.27-5.33 mU/L and free T4 level of 0.61-1.70 ng/dL level within the protocol specified reference range and total T3 level ≤0.94 ng/mL
7. If taking oral estrogen, dose must remain stable for duration of study participation.

4.2 Exclusion Criteria

HFrEF Exclusion

1. Hypertrophic or restrictive cardiomyopathy or uncorrected severe primary valvular disease
2. Arrhythmia that results in irregular heart rate
3. Inability to perform VO2 max exercise testing
4. Clinically significant lung disease as defined by: Chronic Obstructive pulmonary disease meeting Stage III or greater GOLD criteria
5. Treatment with oral steroids within the past 6 months for an exacerbation of obstructive lung disease, or the use of daytime supplemental oxygen
6. Serum creatinine > 3.0 mg/dL
7. History of cirrhosis
8. Chronic intravenous inotropic therapy
9. LVAD use
10. Heart failure hospitalization within the past month
11. Acute coronary syndrome, coronary intervention, or ablation within the past 2 months
12. Cardiac surgery or percutaneous valve or septal defect repair within the past six months
13. Initiation of cardiac resynchronization therapy within the past six months
14. Taking thyroid extract, LT4, LT3, amiodarone, or medication that affects the absorption or metabolism of thyroid hormone (see Appendix)
15. Gastrointestinal condition that affects the absorption of thyroid hormone
16. Current or planned pregnancy within the timeframe of study participation
17. Any medical condition that, in the opinion of the investigator, will interfere with the safe completion of the study

HFpEF Exclusion

1. Hypertrophic or restrictive cardiomyopathy or uncorrected severe primary valvular disease
2. Inability to perform VO2 max exercise testing
3. Clinically significant lung disease as defined by: Chronic Obstructive pulmonary disease meeting Stage III or greater GOLD criteria
4. Treatment with oral steroids within the past 6 months for an exacerbation of obstructive lung disease, or the use of daytime supplemental oxygen
5. Serum creatinine > 3.0 mg/dL
6. History of cirrhosis
7. Heart failure hospitalization within the past month
8. Acute coronary syndrome or coronary intervention within the past 2 months
9. Cardiac surgery or percutaneous valve or septal defect repair within the past six months
10. Taking thyroid extract, LT4, LT3, amiodarone, or medication that affects the absorption or metabolism of thyroid hormone (see Appendix).
11. Gastrointestinal condition that affects the absorption of thyroid hormone
12. Current or planned pregnancy within the timeframe of study participation
13. Any medical condition that, in the opinion of the investigator, will interfere with the safe completion of the study.

4.3 Participant Recruitment

We will leverage an existing recruitment pipeline for heart failure study participants currently used by the Cardiovascular Clinical Research Unit (CCRU). Potential participants will be recruited from the University of Pennsylvania Health System's three Philadelphia hospitals which operate under a single Penn IRB. Depending on effectiveness, the following recruitment modalities may be used

for this study and / or utilizing a telephone recruitment script:

1. Screening and approaching participants who have previously participated in HF and/or aging studies and have expressed interest in continuing engagement with new protocols.
2. Direct Advertising including postings on the Cardiovascular Medicine Divisional website, clinics, and cardiovascular clinical laboratories, postings to be approved.
3. Outpatient Clinic Recruitment: General cardiology clinics, HF clinics, echocardiography laboratory, clinical stress testing laboratory
4. Inpatient clinical service with treating physician approval
5. Real-time participant identification through Penn Chart in the form of Best Practice Advisories (pop-ups). Once identified, team coordinators can approach these potential candidates with physician approval to provide study information for consideration.
6. Agent Insights identification with telephone or clinic approach utilizing an approved telephone script.

Persons who are unlikely to complete study visits due to non-compliance, lack of social support, psychiatric illness or major comorbidities, substance abuse, or other social or logistic circumstances will be evaluated on a case-by-case basis.

4.4 Duration of Study Participation

Screening for participants will require a blood test and review of other medical records and tests. Scheduling the next visit for those that qualify may take up to 4 weeks. Active participation after screening will be ~19 weeks with a ~1-week follow-up phone call after the final visit.

4.5 Total Number of Participants and Sites

Recruitment will end when 56 enrolled participants (28 HFrEF, 28 HFpEF) are randomized. It is expected that 280 participants will undergo informed consent procedures.

4.6 Vulnerable Populations

Pregnant women or women planning to become pregnant will be excluded. Children younger than 18 will not be included because the prevalence and consequences of low T3 syndrome in children with heart failure are not known. In addition, insufficient data are available undermining the ability to judge potential risk in children. No other special vulnerable populations will be enrolled. All participants will be able to provide informed consent.

5 Study Intervention

5.1 Description

The Investigational product is Liothyronine (L-triiodothyronine or LT3) is a synthetic form of the natural thyroid hormone triiodothyronine (T3), available as a sodium salt. We will be using the 5 mcg tablet formulation and a matching placebo for this intervention. Liothyronine Sodium Tablets, USP in the 5 mcg dose and matching placebo will be obtained from Sigmapharm Laboratories and delivered to Kenneth Rockwell, PharmD, MS, Director of Penn's Investigational Drug Service.

Study Drug and Randomization: Study drug randomization and dispensing will be performed through the Penn Investigational Drug Service (IDS). A randomization list for the order of study drug administration (LT3 or placebo) will be created by the IDS using a web-based program,

separately within each study arm - HFrEF and HFpEF. All study drug will be prepared and dispensed by IDS pharmacy. The drug will be delivered directly to the participant at Visits 1 and 3. A pill cutter will be provided at Visit 1 so that the scored tablets can be cut according to titration instruction by the unblinded study physician.

5.2 Study Intervention Regimen

Study Drug Intervention: Oral LT3 or matched placebo will be self-administered three times daily by participants. There will be a weekly titration of active drug/placebo for four weeks based on weekly peak total T3 levels overseen by an unblinded study physician. The T3 levels will be obtained 2-4 hours after the morning LT3 dose. Based upon the T3 result, the unblinded study physician will call the participant with specific dosing instructions to follow immediately throughout the coming week. After four weeks of titration in this manner, the minimum LT3 dose will be 2.5 mcg three times daily and the maximum LT3 dose will be 12.5 mcg three times daily. This dose will be continued for an additional four-week maintenance phase during which weekly T3 levels are not required and the dose will remain steady for these four weeks. After a two-week washout, the participants will cross-over and receive the alternate therapy, following the identical titration scheme to the initial 4-week period with another 4-week dose maintenance phase.

5.3 Receipt

Upon receipt of the drug supply or placebo, an inventory will be performed by the IDS and a drug receipt log filled out and signed by the IDS staff person accepting the shipment. The designated study staff will count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment will be documented in the study files.

5.4 Storage

Liothyronine 5 mcg tablets and placebo will be stored at room temperature in a dry place. They will be kept securely within the IDS pharmacy in a location protected from light and from excess heat or moisture.

5.5 Preparation and Packaging

The preparation, labeling and dispensing of all study drug (LT3 and placebo) will be done by the IDS Pharmacy (available at 215-349-8817 or, for after-hours emergencies, 800-670-3151) in accordance with HUP's Pharmacy Policy and Procedures. Each drug label will include the participant's unique identification number, date dispensed, and directions for use. The study drug ordered for each participant will be delivered individually by IDS to that participant during study visits 1 and 3 in the CHPS Unit and collected and returned to IDS during study visits 2 and 4.

5.6 Blinding

Study drug randomization will be performed through the Penn Investigational Drug Service (IDS). A randomization list for the order of study drug administration (LT3 or placebo) will be created by the IDS using a web-based program, separately for each of the two study arms. The IDS will subsequently perform randomization assignment, and all study investigators, staff, and participants will be masked to treatment vs. placebo assignment. Group assignments will be kept confidential by IDS in order to maintain study blinding. Unblinding will be strongly discouraged and will occur only in the event of an emergency where knowledge of the treatment assignment would affect clinical care, or if recommended by DSMB and/or IRB to address safety concerns.

Otherwise, unblinding will occur only after the study is complete, data collection is complete, and the database is locked.

5.7 Administration and Accountability

Study drug will be dispensed in person at Visits 1 and 3 by the IDS. A pill cutter will be provided to each participant at Visit 1. Sufficient medication for an 8-week period with titrations will be dispensed. LT3 will be dosed three times daily to maintain stable levels.[55]

The initial dose of LT3 will be 15 mcg (5 mcg three times daily: pre-breakfast, mid-afternoon, and bedtime). At least six days (range: 6-9 days) after initiation, the participant will go to a Penn-affiliated laboratory for a peak total T3 measurement 2-4 hours after the morning dose. The following day, the unblinded study physician will call the participant to recommend continuing this dose if the total T3 level is >160 but <180 ng/dL (the upper limit of the reference range) vs. titration to 22.5 mcg (7.5 mcg three times daily) if the total T3 level ≤ 160 ng/dL. Pharmacokinetic data suggest that 5 mcg three times daily should not result in T3 excess in patients with low endogenous T3 levels.[54] If the total T3 level is >180 ng/dL, the dose will be reduced to 7.5 mcg (2.5 mcg three times daily), and the total T3 level will be rechecked the following week.

The process of T3 assessment 6-9 days after a dose change or confirmation and dose titration on the 7th day will continue for an additional 3 weeks, to a maximum dose of 12.5 mcg three times daily. A titration in the placebo group will occur in parallel to LT3 titration. The titration phase will be 4 weeks in duration, followed by a 4-week maintenance phase.

After those ~8 weeks, there will be a study assessment in the CHPS research unit (Visit 2). This will be followed by a ~two-week washout and another assessment (Visit 3). Participants will cross-over and receive the alternate therapy, following the identical titration scheme to the initial ~8-week period and assessment at Visit 4.

5.8 Participant Compliance Monitoring

Adherence will be assessed by direct questioning of study participants during weekly telephone follow-up and study visits. Any evidence of noncompliance will be recorded and participants who are significantly noncompliant with the study treatment regimen may be withdrawn from the study. Determination of noncompliance will be based on investigator judgment. To avoid unnecessary adjustments, un-blinded study physician involved in any medication adjustments will be made aware by study team members of the participants' self-reported adherence to the regimen. Study drug will be collected by IDS at participant study visits 2 and 4 and drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged, signed and dated by the IDS and retained in their records.

5.8.1 Return or Destruction of Investigational Product

At the completion of the study, there will be a final reconciliation of drug distributed, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated in the IDS pharmacy. Drug destroyed on site will be documented in the study files.

6 Detailed Study Procedures

Clinical Evaluation: Visits 1-4. At each visit, a study physician, nurse or delegated study staff will complete a physical exam and review medical history/interim medical history. Vital signs including height (Visit 1 only), weight, blood pressure, heart rate, pulse ox, and respiration rate will be measured. Current medication and changes to medications since prior visit will be recorded.

Resting Energy Expenditure (REE): Visits 1-4. REE will be obtained by indirect calorimetry using the ventilated hood technique (ParvoMedics, Sandy, UT).

EKG: Visits 1-4. 12-lead EKGs will be obtained using the GE Mac 5500 and stored digitally in the MUSE system. EKGs will be read by study investigators blinded to patient and treatment assignment. Variables of interest include heart rate, rhythm, measures of conduction (PR and QRS intervals) and repolarization (QT, QTc).

Echocardiography and Arterial Tonometry: Visits 1-4. Participants will undergo simultaneous Doppler echocardiography and arterial tonometry to assess LV function, arterial load and ventricular-arterial interactions. Both noninvasive assessments are routinely performed in the CHPS unit. From this brief assessment, an array of physiologic measures can be derived after data acquisition, as described below.

Transthoracic echocardiography will be performed using a Vivid I e9 system (General Electric). The protocol will include standard 2D imaging, pulsed-wave Doppler interrogation of LV inflow and outflow tract velocities, and tissue-Doppler interrogation of mitral and tricuspid annular velocities. Simultaneous to LV outflow tract Doppler interrogation, radial and carotid applanation tonometry will be performed using a commercially available system (SphygmoCor EM3, AtCor Medical) with a high-fidelity applanation tonometer (Millar Instruments).[59] Brachial arterial pressures will be measured with a validated oscillometric device (Omron 705IT/HEM-759-E; Omron Healthcare).[60] Radial waveforms will be calibrated with brachial systolic and diastolic pressures. Radial pressures will be used to calibrate the carotid pressure waveform, which serves as a surrogate of the central pressure waveform.[61] Once these data are acquired, the following offline analyses will be performed to generate quantitative physiologic readouts:
LV diastolic function: We will quantify LV diastolic function using the early diastolic (e') mitral annular velocity, averaged from septal and lateral annular measurements.[62] The ratio of mitral inflow early diastolic velocity to mitral annular velocity (E/e') will be used as an indicator of LV filling pressures.
LV myocardial strain: We will quantify peak longitudinal myocardial strain using echoPAC speckle-tracking software (GE Healthcare).[63-66]
Arterial wave reflections and ventricular-arterial interactions: We will implement detailed analyses of arterial pulsatile load using custom-designed software in Matlab (R2011b, MathWorks, Natick, MA) as previously described.[61,67-69] After signal-averaging of pressure and flow waveforms, time alignment of carotid pressure and LV outflow signals will be performed.[61] Pressure and flow harmonics will then be separated into forward and backward components using wave separation analysis.[61,67-69] The sum of forward and backward pressure harmonics yields the forward and backward waves, respectively. Reflection magnitude (RM) will be computed as the ratio of backward to forward wave amplitudes (Pb/Pf).

Kansas City Cardiomyopathy Questionnaire (KCCQ): Visits 1-4. This is a validated 23-item questionnaire that assesses physical function, symptoms, social function, self-efficacy and knowledge, and quality of life.[70] It has been used extensively in multiple heart failure studies.

Hyperthyroid Symptoms from the Thyroid-specific Patient Reported Outcome Measure (ThyPRO): Visits 1-4. This is a validated, thyroid-specific quality of life instrument with 13 scales.[71-73] We will administer 8 items from the Hyperthyroid scale.

Laboratory Assessments: Visits 1-4**.** Non-fasting venous bloods will be drawn, processed, and stored at -80 degrees for future batched performance of TSH, free T4, total T3, reverse T3, and NT-ProBNP at the Penn Diabetes Research Center Radioimmunoassay and Biomarkers Core. At this time, we plan to use the Cobas 4000 analyzer (Roche Diagnostics, Indianapolis, IN) for TSH, free T4, total T3, and NT-proBNP assays and an ALPCO kit for reverse T3. However, assays change over time, and we will use the best commercially available assays in Year 4 for batched analysis.

Cardiac Monitoring Device Monitor: The cardiac monitoring device is a one channel, two-lead cardiac monitor that will provide continuous ECG recording up to 14 days (Figure 2). Since the device is small and lightweight (<1 oz.) and does not require battery changes for the duration of monitoring, patient compliance and comfort level is high. A monitor will be placed at Visits 1 and 3, and participants will be asked to wear the monitor for the first two weeks of each study period. The data are collected for the entirety of the 14 days and are downloaded when the monitors are returned. The data are then analyzed and a summary report generated. This report will be reviewed by Dr. David Lin, electrophysiologist and co-investigator on this protocol, in a blinded fashion. Dr. Lin will also review ICD interrogation data collected during the 17week study period, in a blinded fashion.

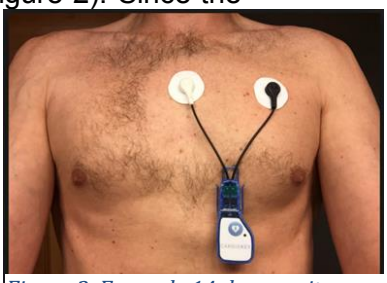

Figure 2. Example 14 day monitor

Actigraph wGT3X+ Waist Actigraph: We will use waist actigraphy. The units are the size of a large wristwatch (Figure 3) and are attached to an elastic belt worn around the waist. Participants will be asked to wear the unit for the last two weeks of each study period (before Visits 2 and 4) except when bathing or charging the unit. The CHPS mHealth service will provide and support the wGT3X+ (maintenance, data downloads, etc.). Activity counts will be recorded in 10 second epochs, downloaded wirelessly, and analyzed using ActiLife software. A Counts per Minute (CPM) value will be derived.

Figure 3. Actigraph.

Peak VO2: Visit 2, 4. Participants will perform a maximal effort supine bicycle exercise test in conjunction with expired gas analysis to assess oxygen consumption (VO2) during exercise, using a Parvo Medics True One 2400 device. We will use a supine cycle ergometer designed for stress echocardiography (Stress Echo Ergometer 1505, Medical Positioning, Inc, Kansas City, MO) and a graded-exercise protocol, with resistance beginning at 12.5 W for 3 minutes, increasing to 25 W for 3 minutes, and then increasing by 25 W every 3 minutes thereafter.

6.1 Schedule of Assessments

	Study Visit 1 (Baseline)						Study Visit 2	Wash-out	Study Visit 3						Study Visit 4	
Week No.	**0**	**1**	**2**	**3**	**4**	**5-7**	**8**			**10**	**11**	**12**	**13**	**14-17**	**18**	**19**
Study Drug Dose (LT3 versus placebo)	**0 mcg**	**5 µg TID**	**2.5-7.5 µg TID**	**2.5-10 µg TID**	**2.5-12.5 µg TID***	**2.5-12.5 µg TID***	**2.5-12.5 µg TID***	**No drug**	**No drug**	**5 µg TID**	**2.5-7.5 µg TID**	**2.5-10 µg TID***	**2.5-12.5 µg TID***	**2.5-12.5 µg TID***	**2.5-12.5 µg TID***	
Visit																
In-person (CHPS)	X						X		X						X	
Informed Consent	X															
Randomization	X															
Lab		X	X	X	X					X	X	X	X			
Phone(complianc		X	X	X	X					X	X	X	X			X
Clinical																
Medical History	X															
Interim Medical							X		X							
Physical	X															
Medication	X						X		X							
12-lead ECG	X						X		X						X	
Laboratory																
Banked**	X						X		X						X	
Local: Total T3		X	X	X	X					X	X	X	X			
Primary																
Peak $V0_2$							X								X	
Secondary																
Transthoracic	X						X		X						X	
Arterial tonometry	X						X		X						X	
Rest	X						X		X						X	
Actigraphy -						X								X		
KCCQ**	X						X		X						X	
ThyPRO	X						X		X						X	
14 day rhythm	+	X	X				^		+	X	X				^	
Study Drug																
Dispense Study Drug	X						!		X						!	

* Maximum dose tolerated

** NT-pro-BNP, TSH, free T4, total T3 and reverse T3

*** Kansas City Cardiomyopathy Questionnaire

\+ Cardiac monitoring device placed ^ Cardiac monitoring device collected

! Medication Collected

6.2 Study Intervention Visits

Initial contact: (-4 Week-0 Week), the participant reviews and signs a screening consent form for an eligibility blood draw (under protocol # 833103) for TSH, free T4, and Total T3 and to collect additional data about medical history, medications, and social habits. Once eligibility is established, the participant will be scheduled for visit 1. In person study visits 1-4 will occur in the

Center for Human Phenomic Sciences (CHPS) outpatient unit.

Baseline/Visit 1: The participant will review and sign the full IRB-approved consent form with the study PI or CoI. A urine pregnancy test will be performed in women with child-bearing potential. A study physician or CHPS nurse practitioner will perform a physical examination including medical history. Weight and vital signs will be measured, current medications discussed, and resting energy assessment will be performed, followed by EKG, echocardiogram, and tonometry. Participants will complete the Kansas City Cardiomyopathy Questionnaire (KCCQ) and Hyperthyroid Symptoms from the Thyroid-specific Patient Reported Outcome Measure **(**ThyPRO) questionnaires. Approximately 2 teaspoons of venous blood will be collected for NT-pro-BNP, TSH, T4, Total T3, and Reverse T3, processed, and stored at -80 degrees. Participants will receive verbal and written instructions on dosing, a pill-cutter, and sufficient study medication for 8 weeks. A 14-day rhythm monitoring patch will be applied to wear home. They will also be provided with a schedule of the lab testing for T3 levels they are required to obtain over the next four weeks, dates for study visits 2, 3 and 4 with all planned study procedures displayed. Participants will be mailed a pre-programmed Actigraph and belt with instructions to place 14 days before visit 2. Study staff will cue them to place at that time during telephone call. Study medication will be dispensed and pill cutter will be provided.

Interim dose titration (Weeks 1-4): Dose titration will be managed by an unblinded study physician, using the titration protocol to achieve a peak T3 level in the upper portion of the reference range. The initial dose of LT3 will be 15 mcg (5 mcg or 1 tablet three times daily: pre-breakfast, mid-afternoon, and bedtime). Six to nine days (>6 half-lives of LT3) after initiation, the participant will be instructed to go to a Penn-affiliated laboratory for a peak total T3 measurement 2-4 hours after their morning dose. The following day, the unblinded study physician will call the participant to recommend continuing this dose if the total T3 level is >160 but <180 ng/dL (the upper limit of the reference range) vs. titration to 22.5 mcg (7.5 mcg or 1 ½ tablet three times daily) if the total T3 level ≤ 160 ng/dL. If the total T3 level is >180 ng/dL, the dose will be reduced to 7.5 mcg (2.5 mcg or ½ tablet three times daily), and the total T3 level will be rechecked the following week. The unblinded study physician and study staff (during telephone follow-up) will instruct regarding pill cutting, and specifically explain the physical quantity of medication participant should take for the week each time a dose is revised. The process of T3 assessment 6-9 days after a dose change or confirmation and dose titration on the ~7th day will continue for an additional ~3 weeks, to a maximum dose of 37.5 mcg (2 ½ tablets three times daily). A titration in the placebo group will occur in parallel to LT3 titration. The titration phase will be ~4 weeks in duration, followed by a ~4-week maintenance phase. Participants will be called the day before each lab visit to assess symptoms, be reminded about the blood draw, and verify study medication dosing. At the day 13 call, they will be reminded to remove the monitoring patch on day 14, to be returned at visit 2.

Weekly calls (Weeks 5-8): Participants will be called weekly to assess symptoms and verify medication compliance. They will be reminded to start wearing the Actigraph attached to the belt over or under their clothing 2 weeks prior to study visit 2.

Visit 2: (~Week 8): Participants will repeat all measures from Visit 1 plus peak VO_2 to assess the effects of their first study medication. They will return the cardio key rhythm monitoring patch, actigraph, and remaining study medication, which will be collected by IDS for a pill count. Actigraph data will be downloaded by designated CHPS staff. Participant will be instructed of two-week medication wash-out, and visit 3 date will be confirmed.

Visit 3 (~Week 10): After a two-week washout, participants will repeat all measures from Visit 1. They will cross-over to the second preparation of study medication (LT3 or placebo) sufficient for

~8 weeks which will be provided to participant by IDS. Participants will once again receive verbal and written instructions on dosing and schedule of lab testing for T3 levels required over the next four weeks. They will repeat interim dose titrations as described for weeks ~1-4 during weeks ~10-14. A 14-day rhythm monitoring patch will be applied. Participants will be provided with a pre-programmed actigraph and belt with instructions to place 14 days before visit 4, assuring study staff will cue them to place at that time.

Weekly calls (~Weeks 10-14): Participants will be called weekly to assess symptoms and verify medication compliance. They will be reminded to start wearing the Actigraph attached to the belt over or under their clothing 2 weeks prior to study visit 4.

Visit 4 (~Week 18): Participants will perform all measurements from visit 1 plus peak VO2 to assess the effects of their second study medication. They will return the cardio key rhythm monitoring patch, Actigraph, and remaining study medication, which will be collected by IDS for a pill count. Actigraph data will be downloaded. Participant will be instructed of follow-up call they will receive at week ~19 and confirmed they have retained the emergency contact number for the study.

Follow-up call (~Week 19): Participants will be called to assess for signs and symptoms of adverse events and to respond to any questions regarding the study and their care related to it.

6.3 Participant Withdrawal

The protocol defined follow-up period per participant will be up to ~19 weeks + 4 weeks from the initial screen. A participant may withdraw from the study for unanticipated reasons.

If there is a participant withdrawal for any reason, clear documentation in the participant CRF's will reflect the circumstance and any follow-up required or recommended by Study Investigator(s). Participants who withdraw early will be requested to attend one final visit to collect investigational product and to follow up regarding adverse events.

6.3.1 Data Collection and Follow-up for Withdrawn Participants

Attempts will be made to obtain at least survival data on these participants up to the end of the participant follow-up period. In the case where the participant withdraws consent from participation in the study, permission to collect survival data will be obtained first. A participant will be labeled as "Lost to Follow-Up" only after the following has been documented:

1. Failure to reach the participant by telephone on 3 separate days
2. Failure to reach the participant's next of kin on 3 separate days
3. Failure to ascertain participant status via direct electronic medical record consultation.

6.4 Early Termination Visits

The protocol defined follow-up period per participant will be up to 19 weeks + time from initial screen. A participant may be withdrawn from the study prior to his or her expected completion date for the following reasons:

1. If the investigator discovers a condition(s) which indicates unacceptable risk to the participant
2. If the participant fails to adhere to the protocol requirements

3. If the participant withdraws consent from participation in the study

If there is a participant early termination for any reason, clear documentation in the participant CRF's will reflect the circumstance and any follow-up required or recommended by Study Investigator(s). For participants who are withdrawn early, every attempt will be made to schedule one final visit to collect investigational product and to follow up regarding adverse events.

7 Statistical Plan

This is an early phase study, and thus our primary outcome is safety, defined by T3 levels and arrhythmias via rhythm monitoring. Our secondary outcomes are defined as efficacy, mechanistic, and other. We have not pre-specified a primary efficacy outcome, as we have not powered our study for efficacy. Instead, we will obtain estimates of central tendency and variance for efficacy to use to power a larger study, as long as the safety parameters support advancing to a larger study. Our other outcomes include clinically relevant efficacy outcomes (peak rate of oxygen consumption [VO_2], quality of life and HF symptoms scores, home activity measured via actigraphy, and NT-proBNP) and mechanistic outcomes (noninvasive assessments of left ventricular function, vascular function, ventricular-arterial coupling, resting energy expenditure, and weight). We will also collect data on hyperthyroid symptoms and thyroid function testing. Each outcome is listed in Table 1 below, along with data collection instrument, type of variable, measure, and psychometric properties.

Table1 Safety and Efficacy Outcomes

Outcomes	Instrument/Source	Type	Measure	Properties
Safety				
T3 levels	N/A	Discrete	% of participants with T3 level above upper limit of reference range (180 ng/dL) at 8 weeks	N/A
Rhythm monitoring	EKG	Continuous and Discrete	Heart rate, rhythm, PR and QRS intervals, QT, QTc	
Rhythm monitoring	Cardiac monitoring device 14-day ECG recording	Continuous and Discrete	% of time in afib, # of VT episodes, # of supraventricular and ventricular ectopic episodes	N/A
Rhythm monitoring	ICD interrogation data	Discrete	Arrhythmias detected	N/A
Secondary (Efficacy)				
Peak VO_2	Parvo Medics True One 2400 device	Continuous	Peak rate of oxygen consumption	N/A
Quality of Life	Validated 23-item Kansas City Cardiomyopathy Questionnaire (KCCQ)[70]	Scale	Each item is rated on a 1-5 Likert scale. Scale scores are transformed to a	Cronbach's α: 0.62-0.90 across 5 domains

			0 to 100 range by subtracting the lowest possible scale score, dividing by the range of the scale and multiplying by 100.	8-week change NS* using a paired t-test
Home activity	wGT3X+ actigraph unit series (ActiGraph, LLC)	Continuous	Physical activity in counts per minute (CPM)	N/A
NT-proBNP	Serum immunoassay, Cobas 4000 analyzer	Continuous	Pg/mL	Analytic range 5-35,000
Secondary Mechanistic and Other				
Echocardiography and arterial tonometry	Transthoracic echocardiography will be performed using a Vivid I system (General Electric). Tonometry will be performed using a commercially available system (SphygmoCor EM3, AtCor Medical) with a high-fidelity applanation tonometer (Millar Instruments)	Continuous	Integrated measures of ventricular and vascular function	N/A
Resting energy expenditure (REE)	Ventilated hood technique (ParvoMedics, Sandy, UT)	Continuous	Indirect calorimetry	N/A
Weight	Standing, calibrated scale	Continuous	Kg	N/A
Hyperthyroid Symptoms	8 hyperthyroid symptoms (validated) from the Thyroid-specific Patient Reported Outcome (ThyPRO) Measure Questionnaire Section[71-73]	Scale	Each item is rated on a 0-4 Likert scale. The average score of items in a scale is divided by four and multiplied by 100 to yield a 0-100 scale, with higher scores indicating worse health status.	Cronbach's α: 0.89 Intra-class correlation coefficient (ICC): 0.89 (0.82-0.93)
Thyroid function tests	Serum immunoassay, Cobas 4000 analyzer ELISA, ALPCO kit (rT3)	Continuous	TSH: IU/L Free T4: ng/Dl Total T3: ng/mL rT3: ng/mL	Analytic range TSH: 0.005-100 Free T4: 0.10-7.77 Total T3: 19.5-651 rT3: 0.02-2
* NS=Not significant				

7.1 Primary Endpoint

This is an early phase study, and thus our primary outcome is safety, defined by T3 levels and arrhythmias via rhythm monitoring (rhythm monitoring and % of participants with T3 levels above the reference range (180 ng/dL) at the completion of each drug).

7.2 Secondary Endpoints

Clinically relevant efficacy outcomes:

- Peak oxygen consumption during a maximal effort exercise test (peak VO_2)
- Quality of life (Kansas City Cardiomyopathy Questionnaire, KCCQ
- Remotely sensed physical activity (actigraph)
- NT-proBNP levels

Mechanistic and other secondary endpoints:

- LV function, arterial load, and ventricular-arterial interactions via simultaneous Doppler echocardiography and arterial tonometry
- Resting energy expenditure
- Weight: At Visits 1-4, weight will be measured in the CHPS unit using a calibrated scale.
- ThyPRO questionnaire section for hyperthyroid symptoms:
- Thyroid function tests: Serum will be drawn for TSH, free T4, total T3, and reverse T3

7.3 Statistical Methods

Preliminary Analyses and Descriptive Statistics: Preliminary data analyses will include estimating descriptive statistics for all baseline measures to characterize the sample from which subsequent inferences may be drawn. Descriptive statistics will include measures of central tendency (mean, median, mode) and variation (standard deviation, interquartile range, range) for continuous measures. Distributional properties of all variables will be examined to determine if variance stabilizing or normalizing transformations should be applied. For dichotomous and categorical variables, measures will include frequencies and percentages. Interim quality analyses will be performed regularly to ensure that data collection and archiving procedures are operating correctly. Descriptive estimates of all measures will be generated for all enrollees at each of the observed time points or period, as well as by intervention group within each time point. Outliers will be accessed via visual inspection of distributions and checked for accuracy. The intervention groups will *initially* be compared within each period, with time invariant covariates only compared for period 1, according to continuous covariates using parametric or non-parametric two-sample t-tests within the general linear modeling framework, depending upon whether or not normality appears to be in question. Levine's tests will be used to assess homogeneity of variance, and normality will be assessed using Shapiro-Wilk tests. Should violations emerge, transformations will be applied or the non-parametric Wilcoxon test will be performed. Additionally, the intervention groups will be compared within period according to categorical covariates using Fisher's Exact tests. Significant differences between groups on these variables will result in their use as control variables in the modeling of outcome.

Primary Analyses - This study will utilize a crossover design, such that 28 patients with HFrEF and 28 patients with HFpEF will be enrolled and randomized to one of 2 sequences, each of which consists of 2 periods (AB/BA design, where A=treatment and B=placebo). Specifically, within each of the two patient groups (HFrEF and HFpEF), 14 participants will be randomized to 8 weeks of placebo, two week washout, followed by 8 weeks of treatment (BA), and 14 participants will be randomized to 8 weeks of treatment, two week washout, followed by 8 weeks of placebo (AB). See Table 2 below for more details. Peak VO_2 and actigraphy will be

examined after placebo and after treatment (two timepoints only; TP2 and TP4). All other outcomes will be assessed before and after placebo and before and after treatment (4 timepoints; TP1-TP4).

The primary outcome is safety (rhythm monitoring and % of participants with T3 levels above the reference range at the completion of each drug). We will be monitoring and summarizing safety data using descriptive statistics. Rhythm monitoring will be described using measures of central tendency and variation, as well as frequencies and percents. Frequencies and percents will be used to describe participants with T3 levels above the upper limit of reference range at the completion of each drug. We will not have separate criteria for stopping by the DSMB. We will also be reporting the number of dropouts/discontinuations as well as the reasons for dropouts/discontinuations.

Table 2. Study Design Overview	
HFrEF patients (n=28)	
BA Arm (n=14)	Phase 1: 8 weeks of placebo → 2 week washout → Phase 2: 8 weeks of treatment
AB Arm (n=14)	Phase 1: 8 weeks of treatment → 2 week washout → Phase 2: 8 weeks of placebo
HFpEF patients (n=28)	
BA Arm (n=14)	Phase 1: 8 weeks of placebo → 2 week washout → Phase 2: 8 weeks of treatment
AB Arm (n=14)	Phase 1: 8 weeks of treatment → 2 week washout → Phase 2: 8 weeks of placebo
TP1=week 0; TP2=week 8; TP3=week 10, TP4=week 18	

The legitimacy of the two week washout period will be evaluated by comparing week 0 (TP1) versus week 10 (TP3) outcome measures within the AB/BA arms for each of the two patients groups. If the outcome measures are within 20% of one another, a clinically significant difference, then we will conclude that the two week washout period is legitimate and we will use data from both phases of both arms (AB and BA) in our estimates of outcomes and effect sizes. If the difference between the outcome measures exceeds 20%, then we will conclude that the two week washout period is not legitimate and we will use data from both phases of the BA arm and only the phase 1 data from the AB arm in our estimates of outcomes and effect sizes. For VO_2 max, we will assess for legitimate washout by 10 weeks after therapy by comparing T4 VO_2 for the AB patients to the T2 VO_2 for the BA patients. If the values are within 20%, then we will perform paired within patient treatment comparisons and test H_0 $\mu=0$.

All **secondary outcomes** are measured on a continuum. Effect size estimates will be based upon differences by phase, as well as differences by timepoint within each phase for each group. Statistical analyses will be performed on an intention-to-treat basis, with data analyzed according to the study arm to which the participant is assigned, regardless of adherence to the assigned intervention (oral LT3 treatment vs. placebo). If the two week washout period is legitimate, the treatment effect will be examined using paired t-tests and non-parametric Wilcoxon sign-rank tests, as appropriate, on the differences between the paired within-participant outcome measures. However, if the washout period is in question, linear mixed-effects model analyses[74] will be conducted, where separate models will be generated for each of the outcome measures. Each outcome measure will be regressed on intervention group assignment (oral LT3 treatment vs. placebo), along with baseline outcome and any other covariates deemed prognostic in preliminary analyses. The fixed effect of interest will be the estimated effect reflecting the difference between intervention groups. Because each response variable represents a repeated measure, nested random effects will be modeled for the outcome of interest for each study participant and for each time period for each participant. The fit of the model will be examined by including a term for either study phase-by-intervention

interaction or autocorrelation of the response variable over time, and compared statistically in terms of the estimated difference between study phases.[75-77] The models will include participant-specific intercepts as random effects, and will assume independent and identically distributed random errors within-participant. Restricted maximum likelihood estimation will be used, and an appropriate covariance matrix will be specified. Model assumptions will be examined (e.g., QQ plots to assess normally distributed residuals for valid Wald tests). All linear mixed-effects models will be analyzed using the SAS PROC MIXED procedure[78] in SAS version 9.4 (SAS Institute, Inc., Cary, NC). A two-sided 0.05 level of significance will be used for both primary and secondary outcomes, without adjustment for multiple comparisons.

7.3.1 Interim Analysis

Since this is a safety study, there will be no interim efficacy analyses. Non-inferential interim analyses will be performed regularly to ensure data collection and archiving procedures are operating correctly. Descriptive estimates of all measures will be generated for all patients at each observed follow-up time point, as well as by intervention group within each time point. Outliers will be visually inspected and checked for accuracy.

7.4 Participant Population(s) for Analysis

The participant population for analysis will be the all-treated population. Any participants randomized into the study that received at least one dose of investigational product will be analyzed. A secondary analysis in the protocol-compliant population will be performed.

8 Safety and Adverse Events

8.1 Definitions

8.1.1 Adverse Event

An **adverse event** (AE) An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in a subject whether or not considered drug or biologic related. An AE can therefore be any unfavorable and unintended sign, symptom or disease temporally associated with the use of the pharmaceutical product.

8.1.2 Suspected Adverse Reaction

A **suspected adverse reaction** (SAR) is any adverse event for which there is a reasonable possibility that the drug caused the event. “Reasonable possibility” suggests there is a causal relationship between the drug and the adverse event. “Suspected adverse reaction” implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

8.1.3 Serious Adverse Event

Serious Adverse Event
Adverse events are classified as serious or non-serious. An adverse event or suspected adverse reaction is considered serious if the investigator or sponsor believes any of the following outcomes may occur:

A **serious adverse event** is any AE that is:

- fatal
- life-threatening: place the participant at immediate risk of death at the time of the event as it occurred
- persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- requires inpatient hospitalization or prolongs hospital stay
- a congenital anomaly or birth defect
- important medical events may not result in death, be life threatening, or require hospitalization, but based on appropriate medical judgement, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the participant, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events. This determination is based on the opinion of either the investigators, and/or DSMB (e.g.if any believe it is serious, it must be considered serious).

8.1.4 Unanticipated Problems(UP) Involving Risk to Participants or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places participants or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.1.5 Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

8.1.6 General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

8.1.7 Post-study Adverse Event

All unresolved adverse events considered probably or definitely related should be followed by the investigator until the events are resolved, the participant is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each participant to report any subsequent event(s) that the participant, or the participant's personal physician, believes might reasonably be related to participation in this study.

8.1.8 Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for additional surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study (Heart Failure) unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the participant, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF) and entered into the study database. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period (through week 19) will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

8.3 Classification of Adverse Events

Severity

Study investigators (PI or Co-I) will use the below scale as a guide for determining the severity, causal relationship to study drug or research procedures, and “expectedness” of an adverse event.

Classification of Adverse Events Regarding Severity Scale	
Grade 1	Mild AE. Awareness of sign, symptom, or event, but easily tolerated; no treatment required
Grade 2	Moderate AE. Discomfort enough to cause interference with usual activity and may warrant intervention. In the latter scenario, AE responds to treatment.

Grade 3	Severe AE. Incapacitating, limiting usual/normal activities or significantly affects clinical status requiring hospitalization or prolongation of hospitalization.
Grade 4	Life-threatening or disabling
Grade 5	Fatal AE

Relatedness

The relationship of each adverse event to the study procedures or to the study drug will be characterized and determined by the study PI or Co-I to and will be classified (related, possibly related, unlikely or unrelated). The AE's will be presented to the DSMB – see DSMP.

Classification of Adverse Events for Causal Relationship to Study Drug	
Not related	There is not a reasonable causal relationship to the drug and the adverse event.
Unlikely related	No temporal association or the cause of the event has been identified, or the drug or biologic cannot be implicated.
Possibly related	There is reasonable evidence to suggest a causal relationship between the drug and adverse event.
Related	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely

Expectedness

The expectedness of an AE or SAR shall be determined according to the participants' underlying conditions, including all cardiac and non-cardiac diagnoses. Given the wide range of comorbidities associated with HF, expectedness will be assessed on a case-by case basis by the PIs.

An **unexpected AE** is any AE occurring in one or more participants participating in a research protocol, the nature, severity, or frequency of which is **not** consistent with either:

1) the known or foreseeable risk of AEs associated with the procedures involved in the research; or

2) the expected natural progression of any underlying disease (including heart failure and the specific comorbidities present in the individual study participant), disorder, or condition of the participant(s) experiencing the AE and the participant's predisposing risk factor profile for the AE.

The following AEs are anticipated, disease-related events in patients with HF:

Unplanned hospitalization, ER visit or clinic visit for worsening HF
Arrhythmias, particularly atrial fibrillation
Sudden cardiac death
Acute coronary syndrome
Cerebrovascular event
Venous thromboembolism
Lightheadedness
Worsening renal function

The following are potential expected side effects of LT3:
Anxiety
Irritability
Tremor
Warmth
Palpitations
Frequent bowel movements
Shortness of breath

8.4 Reporting of Adverse Events and Unanticipated Problems

8.4.1 Adverse Event Reporting Period

The PIs will continuously supervise all aspects of the trial and review the records of the study participants following each visit and at the end of their participation. The period during which adverse events must be reported is defined as the period from the initiation of any study procedures (consent) to the end of the study follow-up (Week ~19 phone contact). Adverse events that do not require expedited reporting (see section 8.5 below) will be reported in summary to the IRB at continuing review. The PIs will be responsible for ensuring that all adverse events are noted, followed and reported to the IRB, and DSMB, as appropriate.

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8.4.2 Expedited Reporting of Adverse Events and Unanticipated Problems

SAEs occurring from signed informed consent to final visit will be captured on the SAE CRF. AEs will be classified according to the guidelines/definitions specified above. Cumulative adverse events are participant to full IRB review at least yearly and DSMB review every 6 months.

Any SAE must be reported by the site investigator or qualified designee within 1 working day of first becoming aware of the event. The IRB should be notified as per institutional guidelines and the NHLBI will be notified per required guidelines (see table below). The DSMB and site IRB, as appropriate, may make an immediate determination about the necessity to modify the protocol, include additional information in the consent form, inform previous participants, temporarily hold enrollment of patients, or terminate the study. The study will proceed only if the DSMB and site IRB all agree on this course of action. The PIs will notify the NHLBI if any of the IRB actions described above occur.

Reporting will be consistent with regulatory and sponsor requirements for the study. At a minimum those events that must be reported to the IRB are those that are:

- Probably or definitely related to study participation and unexpected (report within 10 business days), or
- Probably related, unexpected and event suggests research places subject at greater risk than was previously known or recognized (report within 10 business days).
- Probably or Definitely related death to study participation and unexpected (report within 3 calendar days).

The report will be submitted on a reportable event form and the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Participant number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

What Event is Reported	To Whom is Event Reported	When is Event Reported
Fatal or life threatening unexpected, suspected serious adverse reactions or adverse events	• Local IRB	Within **3 calendar days (**if probably or definitely related & unexpected) – summarize at CR
	• NHLBI, DSMB	Within **7 calendar days/1 week** of initial receipt of information
Non-fatal, non-life-threatening unexpected, suspected serious adverse reactions	• Local IRB	Within **10 business days** of the investigator becoming aware of the problem **(**if probably or definitely related & unexpected) – summarize at CR
	• NHLBI	Within **15 calendar days** of initial receipt of information
Unanticipated Problem that is not an SAE (see above definition of UP)	• Local IRB	Within **10 business days** of the investigator becoming aware of the problem
	• NHLBI	Within **14 calendar days** of the investigator becoming aware of the problem
All Unanticipated Problems	• OHRP (reported by IRB)	Within **30 days** of the IRB's receipt of the report

Within the following 72 hours, the investigator will provide further information (if available and needed) on the serious adverse event or the unanticipated problem in the form of a reportable event form. This should include any diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor.

8.4.3 Follow-up report

The investigators will record follow-up information according to the same process used for reporting the initial event as described above. If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigators will follow all reportable events until resolution, stabilization or the event is otherwise explained.

The DSMB will review detailed safety data approximately every 6 months throughout the study (or at a frequency determined by the DSMB).

8.5 Management of Adverse Events-Criteria for Study Drug Discontinuation

Management of probably related or possibly related AEs may be managed with dose reduction or discontinuation of study drug. Study drug maybe discontinued in the event of an unexpected SAE. In this study population, heart failure is not an unexpected AE or SAE.

8.6 Unblinding Procedures

Any intentional breaking of the blind prior to study completion, which may be necessary, for example, in the case of an SAE that requires knowledge of the treatment assignment for clinical care, or directive of the DSMB will be done in conjunction with the IDS, whose responsibility it will be to notify a designated member of the research team of the individual participant's treatment assignment. Any intentional or unintentional breaking of the blind prior to study completion will be documented and reported to the IRB within 24 hours.

8.7 Stopping Rules

There are no formal stopping rules for the study. However, the study will be stopped if the following criteria occur:

1. The PI discovers a condition or conditions that indicate unacceptable risk to the participants.
2. There is evidence of harm of study-related treatments or procedures to the participants.
3. As directed by the DSMB or IRB for the study.

8.8 Oversight and Monitoring

8.8.1 Data and Safety Monitoring Plan

To ensure the protection of participants' rights, the safety of participants enrolled in the trial, and the integrity and quality of the resulting data this study will be monitored as per the Data and Safety Monitoring Plan (DSMP) developed for this particular study. This DSMP describes the specifications for monitoring, which will be identical between the HFrEF and HFpEF studies. The study shall adhere to the requirements described in the protocol, the International Conference on Harmonization (ICH), FDA Good Clinical Practice (GCP), and SOPs. In addition to PI monitoring, there will be a DSMB. We will also implement an internal monitoring plan.

Study Monitor: The PIs plan to mirror OCRs monitoring standards (and monitoring forms) in efforts to ensure the rigor of safety data collected. The Cardiology Clinical Research Unit (CCRU) has been enlisted to perform this function. The PIs will provide a monitoring plan and associated documents (protocol, Informed Consent Form; ICF), Standard Operating Procedures (SOPs) to the Monitor. The Monitor is qualified by education, experience, and training of Good Clinical Practice requirements as well as regulatory compliance. Details for the internal study monitored are provided in the DSMP.

Data and Safety Monitoring Board: (see section 8.8.2)

8.8.2 Data Safety Monitoring Board

An independent DSMB will be assembled. The DSMB will have four members, including at least

one cardiologist with expertise in heart failure, one cardiologist with expertise in clinical trials, one endocrinologist, and one biostatistician. Penn's conflict of interest policy will be followed. No member of the DSMB will have direct involvement in the conduct of the study. Furthermore, no member will have financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the DSMB. All DSMB members will sign a Conflict of Interest certification to that effect at the time they are asked to participate. Interests that may create a potential conflict of interest should be disclosed to the DSMB prior to any further discussion. The DSMB will determine how to handle a potential conflict. The DSMB can require that a member with a potential conflict not vote or take other means deemed appropriate.

The primary responsibilities of the DSMB will be to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and 2) make determinations concerning the continuation, modification, or termination of the trials. The DSMB will review the study protocol prior to implementation of the study and may request changes to adverse event monitoring procedures.

Interim Analyses and Stopping Rules: Since the proposed study is a safety study, there will be no interim efficacy analyses. Safety will be assessed in real time. We have not proposed stopping rules, and we will allow the DSMB to assess safety without predetermined stopping rules.

9 Study Administration, Data Handling and Record Keeping

9.1 Confidentiality

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed participant authorization informing the participant of the following:

- What protected health information (PHI) will be collected from participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the participant is alive) at the end of their scheduled study period.

9.2 Data Collection and Management

Data for the proposed trial will be collected by the research staff during each study visit using trial-specific and visit-specific data collection forms. All source documents collected in this trial will be housed inside of a locked cabinet in on the 12th floor of the Smilow Center for Translational Research.

Data capture and storage will be accomplished using electronic case report forms (eCRFs) within the framework of the Research Electronic Data Capture (REDCap) project. REDCap is a secure, web-based application designed exclusively to support data capture for research studies. It provides an intuitive interface for data entry with data validation, audit trails for tracking data manipulation and export procedures, automated export procedures for seamless data downloads to common statistical packages and procedures for importing data from external sources. As part of our standard practice, a series of computerized data validation checks will also be programmed

into the REDCap eCRF system to check for missing data, inconsistencies in the data, or data that is out of range.

Once the REDCap database is launched into production mode, study coordinators will be responsible for transmitting participant coded electronic data using eCRFs, which will be subjected to quality checks for accuracy and completeness.

9.3 Records Retention

Study records, including administrative and participant related source and CRFs, will be retained for 7 years after the completion of the research (often marked by a final progress report).

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator and research team will allocate adequate time for such monitoring activities (as described in section 8.8 or by additional regulatory entities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. CHPS unit), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to the Penn Institutional Review Board (IRB), for formal approval of the study conduct.

All participants for this study will be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. See Attachment 1 for a copy of the Participant Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a participant, using the IRB-approved consent form, must be obtained before that participant undergoes any study procedure. The consent form must be signed by the participant or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

11.1 Risks

LT3: LT3 has been in therapeutic use for more than 60 years. Adverse reactions to LT3 are exclusively related to excessive thyroid hormone, which can produce symptoms of thyrotoxicosis and increased risk of atrial tachyarrhythmias. We will be frequently monitoring the thyroid function via blood test during LT3 treatment. Adverse reactions will be averted by a low initial dose of LT3 and gradual dose titration. There will be monitoring for AE's during weekly calls and each patient will have a phone number to call 24 hours for assistance.

Cardiopulmonary stress test: This test is used extensively for research purposes with minimal risk to participants. The most significant risks of the test are dysrhythmias or other cardiovascular complications, which are extremely rare. These procedures will be performed by qualified personnel according to established American Heart Association guidelines,[79,80] Non-revascularized myocardial ischemia, which may increase the risk of complications during exercise testing, is an exclusion criterion for the study.

Participants may feel uncomfortable as a result of pushing themselves during the maximal effort exercise test. Participants will likely feel short of breath and fatigued as a result of the exercise test. Various other complaints, such as nausea, lightheadedness, and other aches and pains are also possible as a result of the maximal effort exercise study. Although exercise testing may result in exhaustion, rarely do people develop abnormal heart rate or heart complications during exercise tests. The risk of this happening is the same as if the participant would exert themselves during stressful situations or during exercise elsewhere.

We will perform EKG, heart rate, and blood pressure monitoring during our exercise test. In addition to the blood pressure (generally increases) and heart rate (generally increases) changes during exercise, we will also monitor arterial saturation. This will be done non-invasively using a pulse oximeter. Of note, oxygen levels can decrease with exercise, even in individuals without significant cardiopulmonary disease.[81,82] If the arterial saturation falls to below 88% ("severe exercise induced hypoxemia"[82]), we will alert the care provider as this may prompt consideration for additional/alternative causes for arterial hypoxemia.

Arterial tonometry, echocardiogram, resting energy expenditure, actigraphy: These are non-invasive procedures and do not have any known significant risks. It is possible that participants may experience mild, temporary discomfort or skin irritation from the tonometry sensor, echo probe, or from wearing the actigraph.

Phlebotomy: The risk of phlebotomy is low. All phlebotomy will be performed by study personnel who are trained and experienced in drawing blood. Risks include minor discomfort, minor bruising, bleeding, hematoma and/or fainting associated with the drawing of blood. There is also a very small chance (less than 1%) of infection at the blood draw site. The amount of blood drawn will be 10 cc/visit.

Cardiac Monitoring Device: Shaving the area where adhesive electrodes will be attached as well as attachment of adhesive electrodes to the participant's skin may cause skin itching and irritation.

Questionnaire (KCCQ, ThyPRO) completion: Participants may become uncomfortable with questions or feel sadness as a result of completing questionnaires.

Confidentiality: There is a potential for a breach of confidentiality. The individual research record kept on each participant will be kept in a locked cabinet exclusively available to PI and study team. Confidentiality will be maintained by assigning an identification code to each participant, entering and retrieving data in computers by code, and keeping codes in a locked file accessible only by investigators. Ongoing commitment to stringently protecting confidentiality will be maintained.

11.2 Benefits

The proposed research is not expected to benefit research participants. It is possible that participants may experience improvement in symptoms of hypothyroidism or heart failure while taking LT3. The major risk is administration of too high a dose of LT3. Potential participants may choose to participate or not to participate.

11.3 Risk Benefit Assessment

New therapies are needed for HFrEF and HFpEF. The risks are reasonable in relation to the importance of the knowledge to be acquired. The proposed studies are essential to determine the therapeutic potential of LT3 in patients with HFrEF.

11.4 Informed Consent Process / HIPAA Authorization

All participants will be provided a consent form describing the study. Obtaining informed consent will be a process whereby information and explanation is provided to each potential participant regarding the research study events and procedures in a private or semi-private location. Sufficient time will be allotted to hear and respond to all potential participant questions and concerns to provide informed decisions about participation in this study. The formal consent of a participant, using the IRB-approved consent form, will be obtained before that participant undergoes any study procedure. The consent form will be signed by the participant and the investigator-designated research professional obtaining the consent. The process of consent will be documented.

12 Study Finances

12.1 Funding Source

This study is financed through a grant from the United States National Heart, Lung, and Blood Institute, National Institutes of Health

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

12.3 Participant Stipends or Payments

Participants will receive $400 for completing the study as payment for time, effort, and inconvenience of being in the study. In addition, they will be provided parking vouchers to park at Penn Presbyterian Hospital.

13 Publication Plan

Study results will be published in peer-reviewed publication. The final, peer-reviewed journal manuscript will be submitted to PubMed Central as per NIH guidelines.

The trial(s) will be registered in www.ClinicalTrials.gov prior to initiation. Registrations will be updated to reflect any protocol amendments during the course of the study. Trial results will be uploaded at the time of publication or within one year of trial completion, whichever comes first. Informed consent documents will include a specific statement relating to posting of clinical trial information at ClinicalTrials.gov. The University of Pennsylvania has an internal policy in place to ensure that clinical trials registration and results reporting occur in compliance with policy requirements.

14 References

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15 Attachments

16 Appendix

Thyroid hormone preparation:
1.Liothyronine

Antithyroid medication:
1. methimazole
2. propylthiouracil

Medication that interferes with LT3 absorption or metabolism or thyroid function test interpretation:
1. lithium
2. amiodarone
3. cholestyramine
4. colestipol
5. colesevelam
6. interferon
7. ipilimumab
8. alemtuzumab

9. pembrolizumab
10. sunitinib
11. sorafenib
12. bexarotene
13. phenytoin
14. carbamazepine
15. rifampin
16. phenobarbital
17. octreotide, somatostatin

16.1 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

16.2 Case Report Forms (CRFs)

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.