Evaluation of the Safety and Efficacy of the OPTIMIZER™ System with Active Fixation Leads in Subjects with Heart Failure Resulting from Systolic Dysfunction: FIX-HF-5

Clinical Investigation Plan

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Sponsor:
Impulse Dynamics NV
6 Werfstraat
Curacao,
Netherlands Antilles

US Sponsor:
Impulse Dynamics (USA), Inc.
30 Ramland Road South
Suite 101
Orangeburg, New York 10962
Tel: 845-359-2389
Fax: 801-601-7832

* Protocol version sent to FDA only and not to the clinical sites.

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Clinical Investigation Plan

I. Title

Evaluation of the Safety and Efficacy of the OPTIMIZER™ System with Active Fixation Leads in Subjects with Heart Failure Resulting from Systolic Dysfunction (FIX-HF-5)

II. Background Information

A. Name and description of investigational product

The investigational product is the OPTIMIZER™ III System, a system capable of delivering non-excitatory cardiac contractility modulation (CCM) signals. These electrical signals are intended to influence myocardial properties in patients with chronic heart failure. The System consists of five major components:

1. An implantable **pulse generator** with specialized internal components that generate the cardiac contractility modulation (CCM) signal (the OPTIMIZER™ III device);
2. Three commercially available percutaneously placed **leads**:
   a. one in the right atrium to sense right atrial activation, and
   b. two in the right ventricle to sense ventricular activation and deliver CCM signals.

For purposes of this study, any commercially available atrial lead can be used. For the ventricular sensing and CCM delivery leads the St. Jude Tendril DX 1388T or 1688T active fixation lead shall be used (or others as qualified by Impulse Dynamics and approved by FDA);

3. A **programmer** which interfaces with the OPTIMIZER™ implantable pulse generator via a standard programming wand, providing the means to set System parameters and assess device diagnostics;

4. A **battery charging system**, consisting of a charger unit, a wand and a patient vest;

5. The **MONITA Hemodynamic Data Acquisition and Processing System** is a data acquisition and analysis system that is used to measure acute changes in dP/dt_{max} in response to CCM signals during the implantation of the OPTIMIZER III System. The implanting physician shall use this information to decide whether or not to proceed with the implantation based upon criteria specified in the protocol below.

B. Summary of findings from non-clinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial

1. Nonclinical studies

a. Basic research

Experimental evidence indicates that electrical signals can modulate cardiac contractility. When cardiac contractility modulating (CCM) signals were applied to isolated rat myocytes, myocyte shortening increased and peak intracellular [Ca^{2+}] increased. This suggested that during CCM signal application there was an increase in intracellular calcium which was the basis for the increase in myocyte contractility.

When CCM signals were applied to isolated rabbit papillary muscles, cardiac contractility modulation reached a steady, stable state within several seconds and recovered within the same amount of time after signal cessation. Peak tension increased, but diastolic tone was not significantly affected. The CCM signal effect was reversed when the polarity of the signal was reversed,

even though the timing and duration of the signal were constant. Intracellular microelectrode recordings showed that signals that increased cardiac contractiltiy were associated with prolongation of the action potential, whereas signals that depressed contractilty caused a decrease in action potential duration. In either case, there was no extra action potential elicited by CCM signals, indicating that their mechanism does not work by any mechanism related to post-extra-systolic potentiation (PESP). Furthermore, when CCM signals were applied in rabbit papillary muscles at 10 times the threshold current level simultaneously with the pacing stimulus, there was no additional force generation. This suggested that the mechanism by which CCM signals enhanced myocardial contractility was not related to recruitment of additional fibers or to recruitment of fibers with higher thresholds.

Hemodynamic data obtained from experiments on 17 healthy, open chest dogs indicated that CCM signals applied to the left ventricle in dual chamber paced hearts induced an increase in cardiac contractility as indexed by an augmentation of $+dP/dt_{max}$. Increases in LV systolic pressures and aortic flow were also observed, with a trend towards reduction in end diastolic pressure.

CCM signals were applied in six heart-failure dogs, transvenously in four dogs and epicardially in the other two dogs. The results indicated an enhancement in LVP, dP/dt_{max} and ESP, in both AAI and DDI pacing modes and in normal sinus rhythm. The CCM signal was applied to 16 DDI paced pigs, resulting in an increase in dP/dt_{max} and an increase in LVP.

Experiments conducted in healthy dogs suggested that CCM signal application to either the left or right ventricle could

improve myocardial contractility with no major adverse effects. Inotropic effects were greater from the right side when the signals were delivered simultaneously to two electrodes inserted into the right ventricular septum.

b. Chronic animal study

A six-month study was conducted in 11 animals to evaluate the safety and performance of the OPTIMIZER™ II System under simulated clinical conditions. This study involved seven treatment animals and four control animals in which OPTIMIZER™ II Systems were implanted. In the treatment animals, the OPTIMIZER™ II System delivered CCM signals to the myocardium for seven equally-spaced one-hour periods every 24 hours. This signal delivery paradigm was similar to the one that will be used in the clinical investigation. In the control animals, the device delivered simulated pacing signals under the same paradigm.

The safety of the System was assessed on the basis of the effects of the CCM signal on myocardial tissue and on lead integrity, the changes in global and regional myocardial function and inotropic reserve and the incidence and severity of adverse events.

At the end of the study, the data showed that the System operated as intended and delivered CCM signals on >90% of beats during the intended periods. The pulse generator turned on and off automatically for the intended periods.

The effects of CCM signals on gross and histologic appearance of the myocardium were indistinguishable from those observed with simulated pacing signals. At lead insertion sites, mature fibrous material devoid of signs of acute inflammation was observed.

There was no effect on histologic appearance of myocardium remote from the lead insertion sites.

The myocardium retained normal inotropic reserve, as evidenced by normal resting function and normal response to dobutamine infusion (assessed by dose-dependent changes in heart rate, dP/dt_{max}, dP/dt_{min}, time constant of relaxation, ventriculography and global and regional echocardiographic assessment of myocardial function). There was no untoward effect of CCM signal delivery over this period of time on lead integrity, as assessed by lead impedances and inspection by scanning electron microscopy.

In aggregate, these data suggested that the device operated as intended and the CCM signals had no identified adverse effects on normal canine myocardium. This study is considered to be appropriate to provide some insight into long term safety of the system because the testing has evaluated a very wide range of myocardial properties with no suggestion of deleterious effects. The finding of no active inflammation around the lead site is a strong indication that there is no ongoing damage created by the signals. Therefore, it is very unlikely that longer term testing in animals would yield any additional or contrary information to what has been identified in this study.

c. Clinical studies

(1) Pilot clinical study

A pilot clinical study of the application of the CCM signal using an external device was conducted with 24 heart failure subjects undergoing EP procedures in Milan, Italy. CCM signals were delivered via a Cardima octapolar catheter inserted into the great

cardiac vein (GCV) via the coronary sinus. The results indicated that CCM signals enhanced hemodynamic parameters. In six subjects with left bundle branch block (LBBB), the application of the CCM signal was applied in addition to biventricular pacing and the effect was additive.

From the left side experience, the primary findings were:

- Improved systolic performance
- No significant change in diastolic function
- Sensation in a small number of subjects, possibly due to the proximity of the CCM electrode to the epicardial nerves
- Difficulty in optimizing lead position in the coronary sinus

These observations provided the motivation for testing whether CCM signals could be effective hemodynamically if delivered to the RV septum. In a second pilot study, as a basis of comparison, eleven subjects had CCM signals applied to the right side of the heart. Primary observations were:

- Improved systolic performance
- No sensation in response to CCM signal/application
- Easily positioned catheters

A larger inotropic effect from the right side was observed when the signal was delivered simultaneously to two right ventricular septal leads as compared to when it was delivered from one electrode alone.

(2) Chronic feasibility study

A safety study of the implantable OPTIMIZER™ System in six subjects with functional NYHA Class III heart failure and baseline ejection fraction of 35% or less by echocardiography was conducted at San Raffaele Hospital in Milan, Italy. Enrolled subjects were evaluated at baseline by echocardiography, a

cardiopulmonary stress test, a 6 minute walk test and 24-hour Holter monitoring.

The CCM leads of the OPTIMIZER™ System were standard pacing electrodes placed percutaneously and guided to the RV endocardial septum. CCM signal amplitude, delay, duration and number of pulses (to a maximum of three) were set during the implantation procedure to achieve a minimum 5% improvement in dP/dt_{max}. Subjects underwent an acute and a chronic phase of monitored CCM signal application or sham signal application, five days per week. Follow-up testing included echocardiograms, 24-hour Holter monitor tests, cardiopulmonary stress tests, 6-minute walk tests and completion of a quality of life questionnaire. All subjects completed participation in the study. There were no clinically significant adverse events in any subject.

(3) Chronic safety and performance study (FIX-HF-3 Study)

A clinical investigation was conducted to evaluate the safety and functionality of the OPTIMIZER™ II System in subjects with New York Heart Association (NYHA) Class III heart failure. Twenty-two subjects underwent OPTIMIZER™ II System implantation. Subjects underwent application of CCM signals for three consecutive hours a day for eight weeks after implantation.

Device interrogations indicated that CCM signals were delivered for the intended 180 minutes per day and on approximately 84±16% (median 90%) of normal sinus beats. CCM signals were appropriately delivered during the relative refractory period (between the QRS complex and the onset of the T-wave) and were suppressed on PVCs as designed.

The data indicated that subject symptoms improved during the study. From Class III at entry, NYHA class decreased in three

subjects to Class I, in 15 subjects to Class II and in two subjects, it was unchanged. Minnessotta Living with Heart Failure Questionnaire (MLWHFQ) scores decreased from baseline value of 41.9±22.2 to 23.6±17.9 (mean reduction of 16.9±21.9, p=0.0027). Ejection fraction increased from the baseline value of 21.4±6.3% to 27.4±7.0% at eight weeks (mean increase 5.9±6.4%, p=0.0006). There was no significant change in heart rate (76±11, median 75), number of PVCs per hour (70.8±176.7, median 21.4), number of runs of non-sustained ventricular tachycardia per hour (0.04±0.10, median 0.02), or the number of premature atrial contractions per hour (17.2±46.8, median 1.7).

There were four deaths (two during the study period and two after study completion), three apparently from cardiac causes in subjects with severe heart failure at high risk of mortality. The fourth death was due to a massive pulmonary embolism caused by documented deep vein thrombosis. A subject with a heart transplant on chronic immuno-suppressive therapy who suffered from chronic rejection and who was treated with the OPTIMIZER™ II system on a compassionate basis but who was followed according to the protocol, died of sepsis. All subjects continue to be followed closely.

Overall, the rate and severity of adverse events were generally expected for patients with severe heart failure within the context of a study of a device-based treatment for heart failure, and were observed with a frequency similar to that of a recent study of biventricular pacing. Seventy adverse events were reported, most commonly palpitations, shortness of breath, dizziness and water retention. Twenty events in 11 subjects were classified as serious and/or severe. Nine events occurring in five subjects were classified as device-related. The most common device-related

events were pocket hematoma and stimulation sensation. In aggregate, these results indicate that the OPTIMIZER™ II System operates as intended, is safe and its use is associated with improvements in symptoms of heart failure.

(4) Increased Duration of Exposure to CCM Signals (FIX-HF-3 Extension Study)

Fourteen of the patients who participated in the study described in (3) above participated in a second clinical study to investigate the effects of increased duration of CCM treatment. In these subjects, the OPTIMIZER II device was programmed to deliver CCM signal for 7 noncontiguous hours per day (7 cycles of 1 hour on, 2 hours 24 minutes off) for 6 months. Upon entry into this increased dose safety study, the clinical status was markedly improved compared to their original baseline status prior to having received CCM treatment. NYHA averaged 1.6±0.5, MLWHFQ averaged 9.6±6.2, 6MW averaged 471±121, peak VO2 averaged 1065±215 ml O2/min (~14.0±2.8 ml O_2/kg/min) and ejection fraction averaged 35±9%. Over the 24 week follow-up period, the clinical parameters were maintained at relatively constant levels, except for peak VO_2 which increased to 1201±343 ml O_2/min (15.8±4.5 ml O_2/kg/min; p=0.02). Medical therapy for heart failure did not change in a majority of patients during this study, and there was an approximately equal number of instances when medication use was increased as when it was decreased.

During the 8 week period of the original FIX-HF-3 study described above, there were 43 adverse events reported in these 14 study subjects. Ten of these events were classified as serious and/or severe. Twelve of the events were classified by the investigators as being definitely, possibly or probably related to

the device. In contrast, during the 24 week period of the present FIX-HF-3 Extension study, there were a total of 43 adverse events of which three were classified as serious and 14 were classified as being definitely, possibly or probably related to the device. Thus, the rate (number of AEs/time) and severity (number of serious AEs) of adverse events was significantly lower in the FIX-HF-3 Extension study than in the original FIX-HF-3 study. The most common adverse events reported during the FIX-HF-3 Extension study were palpitations, dyspnea and pulmonary edema, which are similar to what was reported in the original FIX-HF-3 study.

In aggregate, these results suggest that the OPTIMIZER™ System operates as intended, and appears to be safe when set to deliver CCM pulses for 7 hours/day and that further study of the OPTIMIZER II system in patients with chronic heart failure within the context of randomized, blinded trials to rigorously evaluate the safety and efficacy of this form of treatment are warranted.

C. Summary of the known and potential risks and benefits, if any, to human subjects.

1. Known Potential Risks

The results of bench testing, from preclinical studies using prototype devices in animals and from preliminary clinical studies suggest that acute applications of CCM signals present no undue risk to subjects. However, there are recognized risks associated with the heart failure state itself, with interventional cardiovascular procedures in heart failure patients and potentially with the use of the OPTIMIZER™ system.

a. Death

Class III and IV heart failure patients are at risk for death from their underlying disease, with annual mortality rates ranging from ~20% for Class III patients to as high as ~75% for Class IV patients. With any invasive cardiovascular procedure in heart failure patients there may be added risk of death. Applying appropriate subject selection criteria, using meticulous techniques and providing attentive post-procedure care will minimize the risks associated with these procedures.

b. Risks associated with placement of a Millar catheter

During implantation of the OPTIMIZER™ pulse generator, a Millar catheter will be temporarily placed into the left ventricle in order to measure the peak rate of LV pressure rise (dP/dt_{max}). The catheter will be inserted via standard percutaneous cannulation of a femoral artery. The risks associated with temporary placement of the Millar catheter include infection, bleeding, ventricular arrhythmias, and damage to the femoral artery, aorta or ventricle. These risks are minimized by having experienced operators insert the catheters and by having the procedure performed under fluoroscopic guidance.

c. Risks of implantation of the OPTIMIZER™ pulse generator

The risks associated with implantation of the OPTIMIZER™ pulse generator are similar to those of implanting a permanent pacemaker, which are well characterized and include (but are not limited to) infection, bleeding, pneumothorax, myocardial perforation by the leads and pain at the incision site. Applying appropriate subject selection criteria, using meticulous surgical technique and providing careful post-operative care will minimize the risks associated with these procedures.

d. Arrhythmias and/or palpitations associated with CCM signal application

Arrhythmias may occur as a result of CCM signal application. Arrhythmias may include bradyarrhythmias or tachyarrhythmias as well as ventricular arrhythmias or supraventricular arrhythmias and may be associated with palpitations. These may include sinus bradycardia, complete heart block, junctional rhythm, asystole, sinus tachycardia, atrial fibrillation, atrial flutter, paroxysmal atrial tachycardia, multifocal atrial tachycardia, premature atrial contractions, premature ventricular contractions, nonsustained or sustained ventricular tachycardia, ventricular fibrillation, electromechanical dissociation, or cardiac arrest. Palpitations are commonly reported in patients with heart failure and may or may not be associated with arrhythmias. Safety algorithms intended to minimize the incidence of arrhythmias have been incorporated into the OPTIMIZER™ System.

e. Myocardial damage

Tissue damage may occur at the points where the leads are inserted into the heart muscle. The histologic results of laboratory animal testing have indicated that application of CCM signals through the leads does not induce any clinically significant amount of myocardial damage.

f. Infection

The implantable components of the OPTIMIZER™ System are supplied sterile. The risk of post-implantation infection is minimized by appropriate implantation techniques and care of the wound sites. Infectious complications may include localized infections (infections of the device pocket, femoral cannulation sites, cellulitis, pneumonia, etc) and sepsis.

g. Thromboembolic Events

Thrombosis or embolism may occur as a result of the placement of the leads for the OPTIMIZER™ II System or as a result of the underlying disease. These events may include deep vein thrombosis, renal vein thrombosis, pulmonary embolism and mesenteric thrombosis. Since there is only one additional lead compared to a normal dual chamber pacemaker, the added risk is considered to be not clinically significant.

h. Right or Left Bundle Branch Block

Insertion of pacemaker leads on the right ventricular septum can occasionally cause transient interruption of the specialized conduction system of the heart, which can lead to bundle branch block.

i. Worsened heart failure

CCM signal application is intended to improve the strength of the heart beat and lessen symptoms of heart failure. However, if signal application is ineffective, the subject may experience the typical symptoms present prior to device implantation or may experience the deterioration of symptoms that is characteristic of this disease, including shortness of breath at rest or on exertion, fluid accumulation and pleural effusion, cardiogenic shock, respiratory failure (possibly with the need for mechanical ventilation) or may require alteration of medication doses.

j. Risk of Myocardial Perforation

There is a risk of right ventricular perforation with insertion of any pacemaker lead. If this happened it could result in fluid (including blood) accumulation around the heart (as in a pericardial effusion) that could compromise ventricular function

or even cardiac tamponade. This risk can be minimized by using appropriate, standard insertion techniques by experienced operators.

k. Vascular laceration and bleeding

There is a risk of vascular laceration and bleeding as a result of the implant procedure. These may include bleeding at the femoral access sites and in the pulse generator pocket. This risk can be minimized by using appropriate surgical technique.

l. Chest wall sensation, phrenic or device pocket stimulation

CCM signals may cause chest wall sensation or phrenic stimulation. When these have occurred, they have generally been short–lived and have been resolved by reducing CCM signal voltage. Occasionally an invasive procedure may be required to reposition the leads.

m. Neurologic events

In addition to the risks discussed above, patients with heart failure are at risk for risk of transient ischemic attacks (TIA) and stroke.

n. Potential for OPTIMIZER – ICD/Pacemaker interactions

It is possible that the presence of CCM pulses could be sensed by an ICD which could be interpreted as ventricular tachycardia by the ICD. In such a case, an inappropriate ICD shock could be delivered. Similarly, if a pacemaker inappropriately sensed a CCM pulse for a cardiac depolarization, the pacemaker could be inhibited from delivering treatment during a bradycardia (such as a sinus bradycardia). Device interaction testing has indicated that these do not occur when true bipolar ICD leads are used and when both devices are programmed properly. To minimize this

risk, all personnel involved with programming the OPTIMIZER device are appropriately trained in proper device programming.

o. Surgical revision of the Optimizer System

There is a potential that any system component could malfunction, become damaged, infected, or, in the case of the leads, become dislodged. System component malfunction or other clinical circumstances (eg, sepsis) may require noninvasive corrective actions or possibly even a surgical revision (repositioning, replacement, or removal) of the malfunctioning component(s).

p. General Medical

Patients with heart failure may experience adverse events related to their underlying disease and such may be encountered during the course of the study. These may include hypotension, dizziness, syncope, worsening renal function, worsening liver failure, anemia, etc.

2. Known Potential Benefits

a. CCM signal application

Based upon available evidence from preclinical laboratory animal studies and preliminary clinical safety studies, application of non-excitatory electrical CCM signals to the heart muscle during the absolute refractory period can increase the strength of the heart's contraction. Subjects receiving CCM signal application may experience improvement in myocardial contractility (e.g., increased ejection fraction), which could be associated with improved exercise tolerance, fewer symptoms of heart failure and increased overall quality of life.

b. Medical Management

Subjects will receive a significant amount of attention from medical professionals during the course of this investigation. They will be undergoing cardiac evaluations at frequent intervals. Extra attention will be devoted to ensuring that subjects are receiving the proper types and doses of medications at the proper time. Many studies have shown that patients benefit significantly in how they feel as a result of this type of increased medical surveillance, independent of any benefits that might be provided by the experimental treatment.

D. Description of and justification for the route of administration, dosage, dosage regimen and treatment period.

CCM signals are delivered through commercially available implanted pacemaker leads. The signals have a specified duration and amplitude (voltage), which have been determined in prior pre-clinical and clinical studies. The maximal voltage (7.7V) is delivered unless the subject experiences a side effect (e.g., muscular stimulation, sensation), in which case the voltage may be decreased.

The "dose" of CCM signals is determined primarily by the number of hours per day that the signal is delivered. Results of the chronic safety and performance study that took place in the European Union (described above) suggest that three hours of CCM signal application results in clinical benefit in a majority of subjects. Several subjects initially involved in that study were followed at an increased dose (7 hours of CCM signal per day). The results of that study suggested no increase in risk and potentially mild improvements over the 3 hour per day regimen. Phase I of the present study utilized an intermediate dose of 5 hour/day signal delivery paradigm in order to permit 6 month device longevity of the OPTIMIZER™ II system. Since the safety profile during Phase I of the study has been clinically acceptable and for consistency, the present study shall continue to use the 5 hour/day dose.

E. Statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

This clinical trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

F. Description of the population to be studied.

The patients for whom the OPTIMIZER™ System is indicated are those with reduced ventricular function and symptomatic heart failure. Subjects entered into this investigation will be representative of the patient population with stable, moderate to severe heart failure receiving optimal medical therapy that are likely to benefit from application of CCM signals.

G. References to literature and data that are relevant to the trial and that provide background for the trial.

Pacemaker implantation has been well characterized and is the standard of care for treatment of certain types of cardiac rhythm disorders. The literature related to this therapy is voluminous and readily available. References specific to CCM signal application are listed in **Appendix A**. Cardiac resynchronization therapy (CRT) is applicable to heart failure patients with conduction abnormalities manifested as an increased QRS duration on the body surface electrocardiogram. The clinical studies in which CRT has been evaluated have provided important information for how to conduct studies of CCM signal application and are therefore relevant to the present investigation.

III. Trial Objectives and Purpose

The objective of this investigation is to evaluate the safety and effectiveness of the OPTIMIZER™ System with active fixation leads in subjects with moderate to severe heart failure. Safety and effectiveness endpoints are provided in Section IV below.

IV. Trial Design

A. Primary and secondary endpoints to be measured during the trial

1. The primary effectiveness endpoint of this study, which will be evaluated at the end of six months following the date of scheduled implantation, shall consist of the following parameter:

   Improvement in exercise tolerance, as quantified by ventilatory threshold (VT) measured on cardiopulmonary exercise stress testing (CPX), and evaluated by a blinded core lab. Individual patient response will be based on a $\geq$ 1 mlO_2/min/kg improvement in VT at 6-months compared to baseline.

2. The secondary efficacy endpoints shall be:

   a. Improvement in heart failure class, as assessed by the New York Heart Association (NYHA) classification. NYHA classification shall be assigned by:

      i. blinded on site clinicians according to their standard clinical practice

      ii. by a blinded core lab that evaluates patient responses to a standardized questionnaire.[1]

   b. Improvement in quality of life, as assessed by the Minnesota Living with Heart Failure (MLWHF) Questionnaire.

   c. Improvement in exercise tolerance, as quantified by the six minute hall walk test (6MW).

   d. Improvement in left ventricular ejection fraction as assessed by echocardiography in a blinded core lab.

   e. Changes in left ventricular size as indexed by echocardiographically determined end-diastolic dimension determined by a blinded core lab.

f. Improvements in peak VO_2 consumption and ventilatory efficiency determined on CPX testing.

g. Comparisons of treatment effects separately in subjects whose CHF etiology is ischemic or non-ischemic

h. The need for changes in medical treatment for heart failure (either up or down titration of doses or changes in the types of medications prescribed).

i. Comparison of the primary and secondary safety and efficacy outcome measures in subjects with and without a pacemaker or ICD.

j. Evaluation of the impact of CCM voltage on primary and secondary efficacy and safety outcome measures.

3. The primary safety endpoint of this trial will be:

   The proportion of patients experiencing a composite event of all-cause mortality and all-cause hospitalizations evaluated at 12 months.

4. The secondary safety endpoints of this trial will be:
   a. all-cause mortality
   b. cardiac mortality - any sudden death, or death deemed to be related to heart failure, arrhythmias, myocardial infarction or any other cardiac cause. The cause of all deaths shall be adjudicated by an independent events committee (Section IV.E).
   c. the rate of all-cause hospitalizations
   d. the rate of cardiac-related hospitalizations - any hospitalization during which intravenous diuretics and/or intravenous inotropic agents are administered or any other hospitalization otherwise deemed to be related to heart failure, arrhythmias, myocardial

[1] **Kubo SH, Schulman S, Starling RC, Jessup M, Wentworth D and Burkhoff D**. Development and validation of a patient questionnaire to determine New York Heart Association classification. *J Card Fail* 10: 228-235, 2004.

ischemia or infarction. The cause of all hospitalizations shall be adjudicated by an independent events committee (Section IV.E).

e. overall incidence and seriousness (classified as serious or not) of adverse events, all of which are assumed equivalent between the two treatment groups.

f. changes in the frequency of ventricular arrhythmias as assessed on Holter monitor recordings.

B. Description of the type/design of the trial and a schematic diagram of trial design, procedures and stages

This is a multicenter, prospective, randomized, study in 418 subjects with moderate to severe heart failure despite optimal medical therapy. The study will include a baseline eligibility evaluation followed by randomization to either receive or not receive an OPTIMIZER™ device implant. All patients will be followed for twelve-months (**Figure 1)**. Evaluation of subjects will be documented on electronic case report forms and will include the tests and procedures listed in **Table 1.**

FIGURE 1. Study Overview

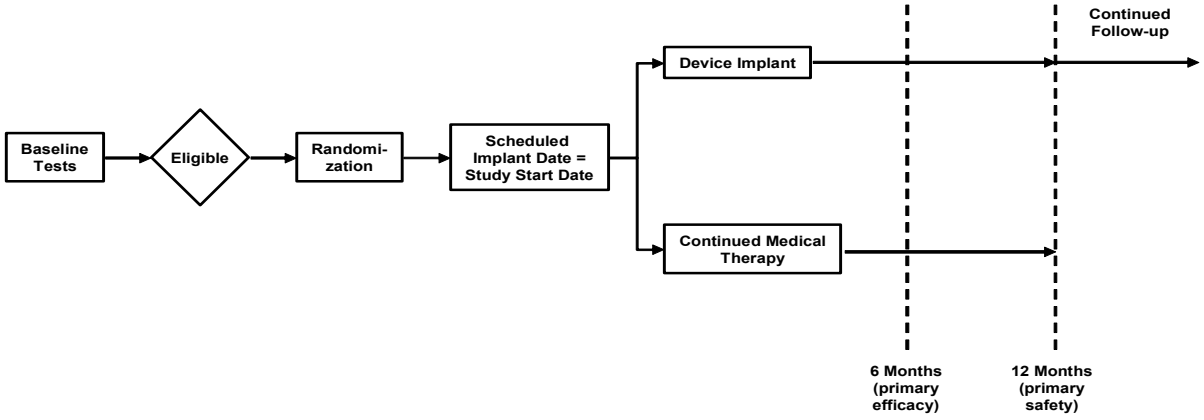

TABLE 1. Schedule of Events

				Follow-Up Schedule (relative to Study Start Date[§])						
Test	**Screening**	**Baseline**	**Implant***	**Week 2 ±2 days[§]**	**+4±1 Week**	**+12±2 Weeks**	**+24±2 Weeks**	**36±2 Weeks**	**50±2 Weeks**	**Every 6 Months***
Informed Consent	X									
History	X			X	X	X	X	X	X	X
NYHA Class (Blinded site clinician assessment)	X					X	X		X	
NYHA Class (Blinded Core Lab Questionnaire)	X					X	X		X	
Medications	X			X	X	X	X	X	X	
Physical Examination	X			X	X	X	X	X	X	
12-Lead EKG		X								
Echocardiogram		X				X	X		X	
MLWHFQ		X				X	X		X	
6-minute walk		X				X	X		X	
Cardiopulmonary Stress Test		X				X	X		X	
24 hour Holter Monitor		X				X	X			
Urine pregnancy test		X					X		X	
Eligibility determination		X								
Randomization		X								
OPTIMIZER™ System Implant*			X							
Chest X-ray*			X							
Optimizer Device Interrogation / Programming*			X	X	X	X	X	X	X	X
ICD Device Interrogation (episodes of VT/VF)				X		X	X	X	X	
Adverse Events, Hospitalizations, and Procedures (as needed) /OPTIMZER device-related SAEs after 50-wks		X	X	X	X	X	X	X	X	X

§ Study Start Date: After completion and satisfying all entry criteria, a date shall be scheduled for OPTIMIZER System implant. This data shall serve as the start date for all subjects. For subjects randomized to CCM Treatment, the OPTIMIZER system shall be implanted on this date. For subjects randomized to the Control group in whom an ICD implant is planned, the Study Start Date shall be the day of the ICD implant. For subjects randomized to the Control group who do not undergo an ICD implant, the scheduled implant shall be cancelled and this date shall serve as the Study Start Date from which all future follow-up visits are scheduled.

* For subjects randomized to ACTIVE TREATMENT group. Subjects are followed every 6 months (+/- 4 weeks) after the 50-week interval for Optimizer Device Interrogation and safety reporting only (All deaths, and OPTIMIZER Device-related SAEs with the corresponding hospitalizations, procedures only).

The details of the Schedule of Events are provided in the **Section VI. A. Treatments to be administered.**

C. Anticipated Rate of Site and Patient Recruitment

Four hundred and eighteen (418) study participants will be recruited from an estimated 50 study sites.

D. Data Safety and Monitoring Board (DSMB)

An independent DSMB shall be established to review results and adverse events in order to provide unbiased oversight of the study. The DSMB shall be composed of members with clinical trial experience in heart failure, electrophysiology and statistics. The sponsor shall work with the DSMB to develop a set of standard operating procedures which shall include the timing and format of regularly scheduled meetings, the format in which data shall be submitted by the data coordinating center to the DSMB members and the format in which the DSMB shall transmit their findings to the Sponsor.

E. Event Adjudication Committee (EAC)

An EAC shall be established. The EAC will be responsible for the review, adjudication and validation of all reported SAEs that occur over the course of the study and the subsequent classification of these complications as related to the device or procedure. The committee shall also adjudicate the cardiac relatedness of deaths and hospitalizations. The EAC shall be composed of independent physicians not otherwise affiliated with the study. The committee will determine a schedule for meeting times based on the expected rate of patient accrual.

F. A description of the measures taken to minimize/avoid bias

This study has been designed to minimize sources of bias so that clinical device performance may be assessed clearly and objectively.

1. Site selection

   The trial will be a multi-center study, with approximately 50 clinical sites located in the United States. Site selection will be based upon investigator and site experience in multi-center studies of heart failure treatments, adequate resources and availability of an appropriate patient population.

2. Randomization

   Subjects will be randomly assigned to one of two treatment groups. Block randomization by site and etiology of heart failure (ischemic versus non-ischemic cardiomyopathy) will be used to ensure balanced enrollment between the two groups.

3. Objective Primary Efficacy Endpoint

   The primary efficacy endpoints of this study are chosen to provide as objective as possible assessment of clinical and physiologic improvements. With regard to the physiologic assessment, ventilatory threshold shall be used to assess efficacy. This parameter is determined by a blinded core laboratory and is considered to be independent of bias and relatively independent of the placebo effect.

4. Core Laboratories

   Core laboratories shall be used to analyze results of cardiopulmonary exercise test, echocardiograms, NYHA and Holter recordings. All analyses shall be performed blinded to treatment assignment. Standard operating procedures (SOPs) for each of the core laboratories are established in collaboration between the Sponsor and each core lab director.

5. Subject accountability

   Every effort will be made to follow all subjects of each cohort to assure as complete a data set as possible.

G. A description of study treatments, the dosage and the dosage regimen of the investigational product.

1. Study treatment

   The trial treatment will consist of the application of non-excitatory cardiac contractility modulating (CCM) electrical signals to the heart muscle.

2. Description of dosage

   CCM signals resemble pacing signals in that they are characterized by a delay, duration and amplitude. Compared to pacing signals, CCM signals are multiphasic, are of wider pulse duration and are higher in amplitude. In this study, the signals will consist of two biphasic pulses ~10 ms in duration (total duration ~20 ms) with amplitude of ~±7.5 V.

3. Dosage Regimen

   In addition to optimal medical therapy, one group of subjects (Treatment Group) shall receive five non-contiguous one-hour periods of CCM signal application per day for the twelve months of the study, with a schedule of one hour ON and three hours 48 minutes OFF.

   A second group of subjects will be assigned to the control group and shall continue to receive optimal medical therapy (Control Group).

4. Description of packaging and labeling

   The OPTIMIZER™ System hardware will be labeled, packaged and shipped in a manner that identifies the System as an investigational device for clinical investigation only, and that protects the device under normal conditions of shipping and handling. The leads will retain their commercial packaging and labeling and will be hand carried or shipped in corrugated shipping boxes.

H. Expected duration of subject participation

The duration of each subject's participation in the main portion of the study is expected to be approximately 13 months. This will include up to one month for screening and baseline testing and a one year primary follow-up period. Following completion of the main portion of the study, patients with an OPTIMIZER™ device shall continue to be followed clinically at approximately 3 month intervals until the FDA has made a determination about the safety and efficacy of the device. The sequence and duration of trial periods are described in **Table 1**.

I. Description of the "stopping rules" or "discontinuation criteria"

1. Individual subjects

   Individual subjects will be discontinued from the study according to Section V.C. Subject Withdrawal Criteria and Procedures Specifying.

2. Entire trial

   The Data and Safety Monitoring Board (DSMB) will review the overall safety aspects of the study and make recommendations regarding the conduct and continuation of the study as necessary. DSMB procedures will be described in the DSMB charter. No stopping rules will be adopted that will allow the trial to stop early to conclude treatment effectiveness.

J. Accountability procedures for investigational products.

Clinical investigators will be trained in the importance of accountability of investigational products. Impulse Dynamics engineers will install any required OPTIMIZER™ System hardware at the site. Disposable components of the System will be hand carried to the site by Impulse Dynamics clinical representatives or shipped directly to the Principal Investigator. Impulse Dynamics clinical representatives will account for the investigational products at the clinical site.

K. Maintenance of trial treatment randomization codes and procedures for breaking codes.

Trial treatment randomization codes will be prepared and maintained by the data management center.

L. Identification of any data to be recorded directly on CRFs (i.e., no prior written or electronic record of data), and to be considered to be source data.

All data pertaining to this study shall be recorded on electronic case report forms. Draft case report forms are located in Appendix C which begins with a summary of which case report forms are required at each study visit. Source documentation shall be made available by the sites to confirm accuracy of data recorded in the case report forms. However, the following data shall be recorded directly on case report forms and in these cases the case report forms shall be considered the source documentation:

1. New York Heart Association Classification questionnaire
2. Minnesota Living with Heart Failure Questionnaire responses

V. SELECTION AND WITHDRAWAL OF SUBJECTS

Four hundred and eighteen (418) subjects will participate in this study.

A. Subject inclusion criteria

1. Subjects who are 18 years of age or older
2. Subjects who are either male or female
   a. Females of childbearing potential must be using a medically approved method of birth control and must agree to continue to use birth control throughout the study, or must be surgically sterilized (tubal ligation, hysterectomy) or post menopausal for at least 1 year.

3. Condition

   a. Subjects who have a baseline ejection fraction of 35% or less by echocardiography.

   b. Subjects who have been treated for heart failure for at least 90 days (including treatment with a β-blocker for at least 90 days unless the patient is intolerant) and are in New York Heart Association functional Class III or IV at the time of enrollment.

   c. Subjects receiving appropriate, stable medical therapy during the 30 days prior to enrollment for treatment of heart failure, consisting of the appropriate doses of diuretics, ACE-inhibitor or angiotensin II receptor blocker and β-blocker. Stable is defined as no more than a 100% increase or 50% decrease in dose.

   d. Subjects who, in the opinion of the Principal Investigator (based on the current guidelines for clinical practice[2]), have a clinical indication for an implanted cardiac defibrillator (ICD) and/or pacemaker, must have an existing device or agree to undergo implantation of such a device unless the patient refuses to undergo the implantation of such device for personal reasons.

   e. Subjects who are willing and able to return for all follow-up visits.

B. Subject exclusion criteria

1. Subjects whose baseline $VO_{2,max}$ is < 9 ml O_2/min/kg

2. Subjects who have a potentially correctible cause of heart failure, such as valvular heart disease or congenital heart disease.

3. Subjects who have clinically significant angina pectoris, consisting of angina during daily life (i.e., Canadian Cardiovascular Society Angina

[2] ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices. Text which can be found at:
http://www.acc.org/clinical/guidelines/pacemaker/incorporated/index.htm

score of II or more), an episode of unstable angina within 30 days of enrollment, or angina and/or ECG changes during exercise testing performed during baseline evaluation.

4. Subjects who have been hospitalized for heart failure which required the use of inotropic support within 30 days of enrollment.

5. Subjects who have a clinically significant amount of ambient ectopy, defined as more than 8,900 PVCs per 24 hours on baseline Holter monitoring.[3]

6. Subjects having a PR interval greater than 275 ms.

7. Subjects who have chronic (permanent or persistent) atrial fibrillation or atrial flutter or those cardioverted within 30 days of enrollment.

8. Subjects whose exercise tolerance is limited by a condition other than heart failure (e.g., angina, COPD, peripheral vascular disease, orthopedic or rheumatologic conditions) or who are unable to participate in a 6-minute walk or a cardiopulmonary stress test.

9. Subjects who are scheduled for a CABG or a PTCA procedure, or who have undergone a CABG procedure within 90 days or a PTCA procedure within 30 days of enrollment.

10. Subjects who have a biventricular pacing system or who have an accepted indication for such a device.

11. Subjects who have had a myocardial infarction within 90 days of enrollment.

12. Subjects who have mechanical tricuspid or aortic valves.

13. Subjects who have a prior heart transplant.

[3] Note: This number is based on the following assumptions:
1. It is desired to deliver CCM signals for ≥70% of the time;
2. CCM signals are suppressed for 3 beats following a PVC. Therefore, if there is one PVC every 13 beats there will be 9 CCM signals delivered (no CCM on the PVC and no CCM for 3 additional NSR beats);
3. If the average HR is 85, there are 115,200 beats/day.
4. If 1/13 of these are PVCs, that equals an estimated 8861 beats/24 hours. The actual percent of CCM signal delivery will depend on whether PVCs occur as singlets, doublets, runs, etc.

14. Subjects who are participating in another experimental protocol.

15. Subjects who are unable to provide informed consent.

C. Subject withdrawal criteria and procedures specifying:

A patient is enrolled in the study after signing the IRB-approved Informed Consent Form. All subjects who sign Informed Consent will be accounted for in the final report of this study. Subjects randomized to the Treatment who withdraw or are withdrawn from the study prior to OPTIMIZER™ device implantation or Control subject who withdraw at any time will be returned to the care of their primary care physician without further study follow-up required (unless specified below). Patients may be withdrawn for the following reasons:

a. Voluntary decision to withdraw made by the subject

b. Subject does not meet one or more of the protocol selection criteria or are unable to complete one or more of the baseline assessments.

c. Non-cardiac intercurrent illness that prohibits the subject from complying with follow-up evaluations.

Good faith efforts will be made to contact all subjects who have received a randomization assignment (including all Phase I patients with an OPTIMIZER device) to ascertain their vital status, important intercurrent medical events and changes in medical condition as reported by the subjects. Every effort will be made to follow all subjects in both cohorts to assure as complete a data set as possible.

VI. Treatment of subjects

A. Treatments to be administered

1. Screening

Potentially eligible subjects will be informed of the relative risks and potential benefits of participating in the study and then asked to sign an informed consent document. A copy of the Informed Consent document is located in Appendix B; this document includes a proposed form to authorize making information available for the purpose of clinical research in compliance with recently enacted patient privacy laws (HIPAA Clinical Research Authorization). It is recognized that each participating institution shall have their own requirements related to the wording of both the informed consent document and the HIPAA form. For each subject, medical history, physical examination, NYHA classification (including a questionnaire for NYHA that will be evaluated by a blinded core lab) and a history (past 90-days) and current usage of medications will be obtained.

2. Baseline Evaluation and Randomization

All enrolled subjects will complete a Minnesota Living with Heart Failure Questionnaire and undergo an ECG, echocardiogram (for site assessment of LV ejection fraction and end-diastolic dimension), a cardiopulmonary stress test (CPX, which shall include assessment of $VO_{2,max}$, RER, ventilatory threshold (VT) and ventilatory efficiency (equal to VE/VCO_2), a 6-minute walk test and a 24-hour Holter monitor test (for assessment of the number PVCs). The 6-minute walk test and CPX tests may be performed on the same day a minimum of 3 hours apart. Females of childbearing potential will undergo a urine pregnancy test within 7 days of the schedule implantation procedure.

If the results of the baseline tests indicate that the subject is eligible for participation, a device implantation date shall be scheduled. The

scheduled implant date shall serve as the Study Start Date for all subjects. The subject shall then be randomized to one of two groups:

a. Treatment Group, in which case the patient shall undergo device implantation on the scheduled implant date. These subjects shall go on to receive CCM treatment for one year as detailed below.

b. Control Group, in which case the subject will be followed with continued medical therapy for one year. For subjects randomized to the Control group who do require an ICD implant based on standard clinical criteria, the ICD implant shall occur on this scheduled date. For patients not requiring an ICD implant, the scheduled implant date shall be cancelled.

3. Study Procedures

a. Treatment

i. Control Subjects

Subjects randomized to the control group shall continue to receive optimal medical therapy and shall be seen according to the same follow-up schedule as those in the Treatment group.

ii. Treatment Subjects

Subjects randomized to active treatment with CCM will undergo implantation of an OPTIMIZER™ pulse generator and associated leads. These subjects will be prepared for device implantation according to the procedure of the institution. The precordial region of the chest (left or right subclavian region) will be prepped and draped using sterile technique. Similarly, an appropriate region for arterial access (such as the femoral region) shall be prepared and draped for cannulated and

introduction of a Millar catheter that will be placed into the left ventricle in a retrograde fashion and connected to a data acquisition and real-time analysis system.

After access to the subclavian or cephalic vein, an atrial lead will be placed transvenously into the right atrium for sensing atrial activity. Two additional leads will be placed transvenously into the right ventricle for sensing ventricular activity and delivering CCM signals. The preferred lead arrangement is for one RV lead to be placed in the anterior septal groove and the other in the posterior groove approximately half way between the base and apex. The second most preferred lead arrangement would be for both leads to be positioned in the anterior or posterior septal groove with a separation of at least ~2 cm.

The minimum acceptable CCM signal effect required to proceed with OPTIMIZER™ pulse generator implantation will be a 5% improvement in dP/dt_{max}. If, after the first CCM signal application, the effect is not 5% or greater, the ventricular leads used to deliver the signal will be repositioned.

If the minimum acceptable signal effect cannot be achieved after several attempts at optimization, the procedure will be terminated. The device will not be implanted and all OPTIMIZER System leads will be taken out. Where clinically indicated and planned, these subjects shall undergo implantation of an ICD and/or dual chamber pacemaker. These subjects will be discharged from the hospital when deemed appropriate by the Principal Investigator and followed according to the

protocol with the exception of Optimizer System device interrogations.

If the minimum acceptable CCM signal effect can be achieved, the OPTIMIZER™ pulse generator will be implanted. Where indicated, subjects may also undergo implantation of an ICD and/or dual chamber pacemaker during the same procedure. Leads which are in place in subjects with a prior ICD and/or pacemaker implant will continue to be used for those devices, but may not be connected to the OPTIMIZER system. To ensure that the OPTIMIZER System does not interfere with proper functioning of the ICD and/or pacemaker, these devices shall be interrogated during application of CCM signals. The main mechanisms whereby device interaction could occur is the potential that the CCM signal is sensed and counted in addition to the QRS as an extra electrical depolarization; this is called double counting. To ensure that this is not the case, the ICD/pacemaker should be programmed to its non-therapy delivering mode and the OPTIMIZER™ System should be activated to deliver CCM signals. The physician then accesses the marker channels of the ICD/pacemaker to check if double counting is present. If so, the physician should modify the ICD/pacemaker parameters (e.g., increase the blanking period) until double counting is no longer evident.

b. Predischarge (for subjects randomized to Treatment Group)

When each of the implanted subjects is stable and suitable for hospital discharge (a minimum 12 hour stay is recommended), he

or she will undergo a chest X-ray according to hospital policy to rule out pneumothorax and to evaluate lead placement.

If the patient has an implanted pacemaker and/or a defibrillator these devices will be activated immediately and remain active. The OPTIMIZER™ pulse generator will be activated prior to hospital discharge with the subject on telemetry. The subject will be observed during this time and device parameters will be adjusted as needed. If the patient has a pacemaker and/or defibrillator implanted, the pacemaker and/or defibrillator will be interrogated to assure proper functioning. The OPTIMIZER™ will be interrogated at the end of the activation period to ensure proper functioning. The OPTIMIZER™ will be programmed in a "monitor only" mode, which means it will not deliver CCM signals, but it will track and record the number of cardiac cycles. If patient has an implanted pacemaker and/or defibrillator the pacemaker/defibrillator will remain active. At the discretion of the Principal Investigator, the subject may be observed for additional days of device activation in the hospital prior to discharge.

Prior to discharge, patients may be introduced to the battery charging system and provided a comprehensive overview on the use of this equipment. If not at discharge, this training will at least be provided when CCM therapy is turned on (Week 2 Follow-up visit).

c. Week 2 Follow up

Two weeks after the OPTIMIZER System implant or 2 weeks following study start date for control subjects, each subject will return for follow up. This visit shall include an interim medical history, a medication review, and a physical examination. For

patients randomized to the treatment arm the pulse generator will be interrogated to confirm proper functioning and parameters shall be adjusted as needed. At this time, the OPTIMIZER System shall be activated (turned ON). These subjects will also be educated on the use of the OPTIMIZER System charger.

d. Weeks 4, 12, 24, 36 and 50 following Study Start Date

Subjects randomized to active treatment will receive CCM signals for five one-hour periods equally spaced over the course of each day. Subjects in the control group will receive continued optimal medical treatment.

All subjects will return to the hospital for follow-up at weeks 4, 12, 24, 36 and 50 following Study Start Date. Each visit shall include an interim medical history, a medication review, and a physical examination. On study Weeks 12, 24 and 50 following Study Start Date, a blinded clinician will perform a site-based NYHA classification and administer a questionnaire for core lab determination of NYHA classification, a 6-minute walk, cardiopulmonary stress test, an echocardiogram and a MLWHFQ will be obtained in addition to device interrogations. 6-minute walk and CPX may be done on the same day a minimum of 3 hours apart. On Weeks 12 and 24, subjects will undergo a Holter monitor examination.

The ICD will be interrogated at 12, 24, 36, and 50-weeks to ascertain proper functioning of the device, in subjects with an ICD. For all subjects, medical regimen for heart failure treatment shall remain fixed unless clinical circumstances dictate otherwise; changes in medical regimen shall be elicited and recorded during the scheduled follow-up visits.

All female subjects shall be asked to notify the Investigators in the event of pregnancy. In addition, women of child bearing potential using medical birth control who receive an OPTIMIZER System implant shall be asked to undergo a pregnancy test at the week 24 and 50 visits. If a patient randomized to device treatment becomes pregnant the device will be turned off. Any study patient who becomes pregnant will continue to be followed for evaluation of safety endpoints.

e. Post Study Follow-Up

Following the 50 week follow up, subjects in the Control group shall resume routine follow-up from their primary care providers. Subjects in the Treatment group can continue to receive treatment with CCM signals. These patients shall be seen at ~6 month intervals at the investigational site. These follow-up visits shall include an Optimizer device interrogation and reporting of any Optimizer device-related serious adverse events (and corresponding hospitalizations and procedures, if any) and all deaths. These visits shall continue until FDA has made a determination of device safety and efficacy. In the event that the study is terminated prior to approval, the device is found to be ineffective or at the request of the patient, the device can be removed. Alternatively, the device can be left in place and deactivated; in this case, the device charger would be retrieved from the patient in order to eliminate the possibility of further use of the device.

f. Device retrieval in case of subject death

In the event that a study participant dies, every attempt will be made to secure permission from the family to retrieve the device.

In such cases, the device shall be shipped to the sponsor where it shall be inspected and interrogated.

B. Treatment of Subjects Enrolled in Phase I of this Study

Phase I of this study was designed as a double blind study in which all subjects underwent OPTIMIZER II System implant and were randomized for 6 months to either receive or not receive CCM treatment. This is then followed by a 6 month period of open label CCM treatment. Fifty patients were enrolled in this phase at 10 investigational sites. Treatment of patients enrolled in Phase I is further detailed in Appendix D. In brief, these patients shall be offered an OPTIMIZER III device when the battery of the OPTIMIZER II system becomes depleted.

C. Medications/treatments permitted (including rescue medication) and not permitted before and/or during the trial

Subjects will remain on their initial medication regimens throughout the study, unless clinical circumstances dictate a change. There are no restrictions on the types of medications that may be used during the trial.

D. Procedures for monitoring subject compliance

Clinical monitoring will be performed by/or under the management direction of the Impulse Dynamics Clinical Affairs Department.

VII. Assessment of efficacy

A. Specifications of efficacy parameters

The primary efficacy parameter shall be:

- Change in ventilatory threshold as assessed by cardiopulmonary stress test as evaluated by a blinded core lab.

The secondary efficacy parameters shall include:

- Change in heart failure class, as assessed by the New York Heart Association (NYHA) classification. NYHA classification shall be assigned by:

  - the blinded site clinician according to their standard clinical practice
  - by a blinded core lab
- Change in Quality of Life, as assessed by the Minnesota Living with Heart Failure Questionnaire
- Change in exercise tolerance, as assessed by the six-minute walk test
- Change in left ventricular ejection fraction, as assessed by echocardiography and determined by a blinded core lab
- Changes in left ventricular end-diastolic dimension as assessed by echo and determined by a blinded core lab
- Changes in peak oxygen consumption and ventilatory efficiency as assessed by cardiopulmonary stress test
- Comparisons of treatment effects separately in subjects whose CHF etiology is ischemic or non-ischemic
- Changes in medical treatment for heart failure (either up or down titration of doses or changes in the types of medications prescribed).
- Comparison of the primary and secondary efficacy and safety outcome measures in subjects with and without a pacemaker or ICD.
- Evaluation of the impact of CCM voltage on primary and secondary efficacy and safety outcome measures.

B. Methods and timing for assessing, recording and analyzing efficacy parameters

The timing of efficacy parameter assessments, as summarized in **Table 1**, will be at approximately three-month intervals.

VIII. Assessment of safety

Although results of prior pre-clinical and clinical studies have suggested means by which CCM signals may improve symptoms for patients with heart failure, it is acknowledged that the actual mechanism of action is not known. This is not atypical for investigation of new treatments in medicine, including devices and pharmacologic agents. As for any new treatment, whether the mechanism is known or unknown, assessment of safety rests on careful ascertainment and documentation of adverse effects within the context of a randomized, controlled clinical trial.

A. Specification of safety parameters

The safety of the OPTIMIZER™ System will be assessed by evaluating the incidence and seriousness of adverse events (see section IX.A.2 for statistical analysis plan). The primary safety endpoint shall be the proportion of patients experiencing a composite event of all-cause mortality and all-cause hospitalization by the 12 month visit.

An adverse event is defined as any undesirable clinical occurrence in a subject, including death. Examples of adverse events that could occur as a result of the surgical procedure and implantation of the device components are listed below in hierarchical order of clinical severity:

1. Death
2. Arrhythmias (tachy- or bradycardias)
3. Stroke or transient ischemic attack (TIA)
4. Respiratory failure
5. RV perforation

6. Bleeding
7. Infection
8. Pleural and pericardial effusion
9. Pneumothorax

Examples of additional adverse events that could occur as a result of the subjects' underlying disease (i.e., heart failure) or CCM signal application are listed below in hierarchical order of clinical severity:

1. Abnormalities of cardiac function
2. Worsening of heart failure
3. Myocardial tissue damage
4. Chest pain

B. Serious, Device Related and Unanticipated Adverse Event Definitions.

Adverse events that occur during this study may be associated with the implant procedure, or specifically associated with the use of the device. An adverse event will be considered to be device-related when, in the judgment of the Principal Investigator, there is a logical connection between the use of the device and the occurrence of the event, above and beyond the study procedure itself.

A serious adverse event is any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization, prolongation of existing hospitalization or invasive treatment, results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect. An unanticipated adverse device event is defined as any serious adverse effect on the health or safety of a subject or any life-threatening problem or death caused by or associated with the device, which was not listed in the Investigational Plan or the labeling for the device.

A serious device-related adverse event is any serious adverse event (as defined above) that is considered definitely related to the Optimizer System. An adverse event will be considered device-related when, in the judgment of the Principal

Investigator, there is a logical connection between the use of the device and the occurrence of the event, above and beyond the study procedure itself. Examples include:

- Optimizer lead failure (dislodgement, fracture) requiring surgical revision
- Optimizer IPG failure requiring surgical revision
- Optimizer pocket erosion requiring surgical revision
- Pocket stimulation secondary to CCM, requiring surgical revision

C. Procedures for recording and reporting adverse events and intercurrent illnesses.

The Investigator shall report all adverse events to Impulse Dynamics and to the reviewing IRB (according to Hospital policy). All device malfunctions and serious adverse events, including, but not limited to events associated with prolongation of hospitalization, and/or a new hospitalization or death shall be reported to Impulse Dynamics within 24 hours of the Investigator learning of the event. Impulse Dynamics will report serious adverse events to the Data Safety and Monitoring Board (during the 1 year study only) and to the FDA as required.

D. Type and duration of follow-up of subjects after adverse events.

All subjects experiencing serious adverse events will be followed as required by their condition. Impulse Dynamics will investigate any anticipated or unanticipated serious adverse effect or subject death. If it is determined that the adverse event could present an unreasonable risk to other subjects, all investigations or parts of investigations presenting that risk will be terminated. Investigation of the event and notification of study termination will occur within five working days after notice of the effect is received at Impulse Dynamics. The terminated investigation will not be resumed without IRB approval.

IX. Statistical Considerations

A. Description of the statistical methods to be employed

1. Primary efficacy analysis

The primary efficacy analysis will compare responder rates between the Treatment and Control groups at the 6-month follow-up visit. The primary outcome measure will be:

- change from baseline in the ventilatory threshold (VT) determined on cardiopulmonary stress testing

Individual patient response will be defined as an increase of ≥ 1 **ml O_2/kg/min** in VT at 6 months as compared with baseline. Responder rates will be calculated and compared between the treatment and control groups based on both the intent-to-treat population and the per-protocol population using a one-sided binomial comparison with an alpha of 0.025.

The statistical hypothesis to be tested is:

$$H_0: \pi_c \geq \pi_t \quad \text{vs.} \quad H_A: \pi_c < \pi_t$$

Where π_c is the proportion of patients in the control group that have ≥ 1 ml O_2/kg/min improvement in VT at 6 months from baseline and π_t is the proportion of patients in the treatment group that have ≥ 1 ml O_2/kg/min improvement in VT at 6 months from baseline.

2. Primary Safety Analysis

The primary safety analysis shall evaluate the composite event rate of all cause mortality and all cause hospitalization at 12 months. The statistical hypothesis shall be that the proportion of patients in the treatment group where an event occurs by 12 months will be non-inferior to the proportion of patients where an event occurs by the 12 month visit in the control group.

The statistical hypothesis to be tested shall be:

$$H_0: \pi_t > \pi_c + \delta$$

vs.

$$H_1: \pi_t \leq \pi_c + \delta$$

where δ=0.125 (clinically insignificant difference) and π_c is the event rate in the control group and the π_t is the event rate in the treatment group.

The statistical test to be used shall be the Blackwelder non-inferiority test and will be evaluated based on the intent-to-treat patient population and the per protocol patient population. Censoring is expected to be minimal, but in order to determine if there are different patterns of mortality between groups, Kaplan-Meier curves will also be constructed, with Log-rank tests used to determine statistical significance between groups.

The nature, frequency, and seriousness of adverse events between the two groups shall be compared using descriptive summary statistics.

3. **Justification of sample size**

Results of prior studies of CCM and biventricular pacing in which VT has been employed as an endpoint provide estimates for standard deviations of changes and standard deviations of absolute values that may be observed in the present study.

For the safety endpoint, the composite event rate of all cause mortality and all cause hospitalization at 12 months **shall be used.** Based on prior studies with cardiac resynchronization therapy and preliminary experience with CCM, if we assume a total event rate (mortality or hospitalization for any cause) of 50% (a conservative estimate for sample size purposes), an alpha of .05, 80% power and a delta of 12.5%, 198 patients per group would be needed to show non-inferiority between groups at 12 months. With regard to this analysis, we do not expect any dropouts (i.e., we expect to be able to account for mortality and hospitalizations in all patients enrolled); however, adjusting for a

potential 5% loss to follow-up results in a total sample size of 418 patients (209 per treatment group).

For the efficacy endpoint, the response rate based on a ≥ 1 ml O_2/kg/min increase in VT at 6 months compared with baseline, will be compared between the two treatment groups.[4] Due to the natural progression of heart failure, we anticipate VT may actually worsen in a considerable portion of control patients. Furthermore, because of the anticipated variability in test results and based on prior studies of heart failure, including those on CRT (e.g., the MIRACLE study, Abraham et al, N Engl J Med 2002;346:1845-53 and the Medtronic InSync Biventricular Pacing System's Summary of Safety and Effectiveness P010015) it is also expected that a certain number of control patients will meet the success criterion. It is estimated that that a reasonable estimate of the responder rate would be ~20% in the control group based on a preliminary analysis of limited clinical data collected in Europe and prior studies of heart failure. We expect to observe a relatively large difference (*e.g.,* 30% or larger) between groups. In this case, the sample size shall be determined based on the safety analysis. Even after allowing for a 5% lost to follow-up for efficacy purposes (*i.e.,* which would result in 198 evaluable patients) this sample size would provide sufficient power to detect a 13% or greater difference in responder rates between groups if a 20% responder rate was observed.

Thus, in order to have adequate power for all study endpoints, the study will enroll 209 patients per treatment group.

4. Secondary efficacy analyses

[4] A difference in VT of 1 ml O_2/kg/min is justified as being clinically significant based on prior studies of cardiac resynchronization therapy showing that there is an approximately 1 ml O2/kg/min change in response to that approved therapy (Auricchio et al. J Am Coll Cardiol 2003;42:2109-16)

The secondary analyses will include:

a. Comparison between groups of the change from baseline in New York Heart Association (NYHA) classification. NYHA classification shall be assigned by:
   i. blinded on site clinicians according to their standard clinical practice
   ii. by a blinded core lab that evaluates patient responses to a standardized questionnaire.[5]

b. Comparison between groups of the changes from baseline in quality of life, as assessed by the Minnesota Living with Heart Failure (MLWHF) Questionnaire.

c. Comparison between groups of the change from baseline in exercise tolerance, as quantified by the six minute hall walk test (6MW).

d. Comparison between groups of the change from baseline in left ventricular ejection fraction as assessed by echocardiography in a blinded core lab.

e. Comparison between groups of the change from baseline in left ventricular size as indexed by echocardiographically determined end-diastolic dimension determined by a blinded core lab.

f. Comparison between groups of the change from baseline in peak VO_2 and ventilatory efficiency determined on CPX testing.

g Comparisons of treatment effects separately in subjects whose CHF etiology is ischemic or non-ischemic

h. Comparison between groups of the change from baseline in medical treatment for heart failure (either up or down titration of doses or changes in the types of medications prescribed).

[5] **Kubo SH, Schulman S, Starling RC, Jessup M, Wentworth D and Burkhoff D**. Development and validation of a patient questionnaire to determine New York Heart Association classification. *J Card Fail* 10: 228-235, 2004.

i. Comparison within the treatment group of the primary and secondary safety and efficacy outcome measures in subjects with and without a pacemaker or ICD.

j. Evaluation of the impact of CCM voltage on primary and secondary efficacy and safety outcome measures.

5. Other Analyses

Baseline comparisons between the treatment and control groups will be made with respect to baseline evaluations (including NYHA Class, peak VO2, MLWHFQ, initial medications and additional implanted devices). If any significant differences are observed in the aforementioned baseline factors or other covariates, all primary and secondary analyses will be repeated with an adjustment for the significant factors.

Additionally, an exploratory comparison for treatment effects across sites will be performed along with a statistical comparison using a chi-squared test for homogeneity.

B. Number of subjects planned to be enrolled

Based upon the power calculations in Section IX.A.3 above, 418 subjects will be randomized in a 1:1 ratio between the two groups.

C. Study Termination

The study shall be considered complete approximately 50 weeks after the last study subject is randomized, when all non-withdrawn subjects have completed the Week 50 follow-up. Patients with an implant who choose to continue CCM therapy shall continue to be followed every six months until FDA has completed their review of this study.

D. Procedure for accounting for missing, unused and spurious data.

Subjects must have baseline measurements of VT to be eligible for the study. Every attempt will be made to record the endpoints on all subjects at all follow-up points, but especially at Week 24 (the primary efficacy endpoint assessment) and 50 weeks (the primary safety endpoint assessment). An intent-to-treat analysis will be performed on the primary efficacy and safety endpoints and will include all patients randomized, regardless of whether patients withdrew prior to study completion. The main reasons for withdrawal are anticipated to be failure to reach ≥ 5% improvement in dP/dtmax during the system implant procedure (for patients randomized to treatment) and voluntary decision by the patient (for patients randomized to control). Imputation of missing data will include a conservative scenario and missingness patterns will be compared across treatment groups. Where missing data are present, a worst case analysis (control subjects assumed to satisfy success criteria and treatment subjects assumed to fail success criteria) shall also be performed for the primary safety and efficacy analyses.

E. Procedures for reporting deviations from the original statistical plan.

Deviations from the original statistical plan will be reported at the time that the statistical report is issued.

F. Selection of subjects to be included in the analyses.

All subjects will be accounted for in the analyses (See **Section 9.E**.).

X. Direct access to source/data documents

The investigators and institutions will permit trial-related monitoring, audits, IRB review, and regulatory inspections, providing direct access to source/data documents.

XI. Quality control and quality assurance

Quality control and quality assurance will be the responsibility of the Impulse Dynamics clinical representatives.

XII. Ethics

Heart failure is a prevalent health problem throughout the world. Development of therapies to improve heart function to relieve symptoms, reduce hospitalizations and improve survival is a high priority in cardiovascular medicine.

Studies in animals have demonstrated the safety of the OPTIMIZER™ System with commercially available active fixation leads and the performance of the CCM signal in improving ventricular function. Results of preliminary clinical studies suggest that brief applications of CCM signals do not pose an unreasonable risk to heart failure subjects. The present study represents the next step in the evaluation of this device. The study is justifiable because the potential benefits of using the device outweigh the risks to participating subjects.

Prior to the initiation of the study, the Principal Investigator will provide Impulse Dynamics with a copy of the Patient Informed Consent document that has been approved by the IRB at the investigational site. Before enrollment, each subject will be informed of the overall requirements and potential risks and benefits of the study and his/her written consent will be obtained.

XIII. Data handling and record keeping

All study data will be entered directly into an electronic data capture system (EDC) by clinical site personnel throughout the course of the study. Access to clinical study information will be based on individuals' roles and responsibilities and will be controlled by login and password provided by the database administrator. The application provides hierarchical user permission data entry, viewing, and reporting options. For optimum security, the system operates Secure Socket Layer (SSL) 128-bit encryption protocol over Virtual Private Networks. This application is designed to be in full compliance with the FDA's Code of Federal Regulations (CFR) Number 21 Part 11, Electronic Records and Electronic Signatures, the FDA's Guidance: Computerized

Systems used in Clinical Trials, and the Privacy Rule of the Health Insurance Privacy and Portability Act of 1996 (HIPAA)

Original source documents will remain at the sites for data verification during monitoring visits. De-identified source documents may be retrieved for presentation to oversight committees when requested. The documents will be maintained in the Impulse Dynamics Regulatory Affairs office in Orangeburg, New York. Database development and management shall be performed by:

Medidata
79 Fifth Avenue
New York,
NY, 10003
Tel: 212 918 1800
Fax: 212 918 1818

APPENDIX A

CCM References

Impulse Dynamics - Articles

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Appendix B

Subject ID Number:___-_____

Evaluation of the Safety and Efficacy of the
OPTIMIZER™ System with Active Fixation Leads in
Subjects with Heart Failure Resulting from Systolic Dysfunction:
FIX-HF-5

INFORMED CONSENT

Introduction

Your doctor has explained to you that your heart strength is decreased and this may be causing you to experience tiredness and shortness of breath. This condition, called *heart failure,* is usually treated with medications to improve the strength of the heart muscle and reduce the amount of work the heart has to do. However, medications are not always successful in making heart failure patients feel better. A new experimental medical device has been developed to improve heart strength using electrical signals applied to the heart. The experimental medical device is called the OPTIMIZER™ System. The experimental treatment delivered by the OPTIMIZER™ System for stimulating the heart muscle with an electrical signal is called cardiac contractility modulation (CCM) treatment.

Research

You are being asked to consider voluntary participation in a research study of the CCM treatment with the OPTIMIZER™ System sponsored by IMPULSE DYNAMICS (USA), Inc. The purpose of the study is to determine whether the CCM treatment improves the way you feel. We would like to give you all the information necessary to help you make an informed decision about participating in this research study. Before you give your consent please read the following information carefully.

The information given here is not intended to be a substitute for the opinion of your doctor, who will answer all your questions about this study.

Expected Duration of Study Participation

Your participation in this study is expected to be approximately 13 months. This will include up to one month for screening and baseline testing with a one year follow-up period. If you receive an OPTIMIZER System implant, you will be asked to return for follow-up every 3 months for as long as you have the device in place and choose to keep it active until the FDA completes their review of this study. This follow up may take up to 5 years.

Study Procedures

Certain medical tests will be performed to determine if you are eligible to participate in this study. These tests include a physical examination with a medical history; an electrocardiogram (to check the electrical activity in your heart); two different types of stress tests (one test performed on a treadmill while the oxygen in your breath is analyzed and a second test to see how far you can walk on flat ground), an echocardiogram (to check the strength of your heart), two questionnaires that ask you about your heart failure symptoms and a 24-hour Holter monitor test (a tape recording of your heart rhythm over the course of an entire day). If you are a woman of childbearing potential, a pregnancy test will be done within 7 days of scheduled implant to make sure that you are not pregnant; in addition, you must agree not to become pregnant as long as you are in this study. Women of childbearing potential must be using a medically approved method of birth control such as an IUD, surgical sterilization (hysterectomy, tubal ligation), or must be post-menopausal for at least one year.

If the results of these tests indicate that you are eligible to participate, you will be randomly assigned (like flipping a coin) to one of two groups: either a group that receives an OPTIMIZER System or a group that does not receive the OPTIMIZER System. Regardless of which group you are in, you will continue to be followed closely to ensure that you are receiving optimal medical therapy for your heart failure.

If you are randomized to receive the OPTIMIZER System, you may require additional testing in accordance with the procedures followed by your institution. These tests may include blood testing, urinalysis, and a chest x-ray. These procedures vary at each institution, so your doctor will discuss them with you. At the beginning of the implant procedure, your doctor will temporarily place a catheter inside the main pumping chamber of your heart (left ventricle) through a small incision in an artery in your groin. This catheter will be used to measure the effects of CCM treatment on your heart. If the effects of the CCM treatment do not reach a certain level the OPTIMIZER System will not be implanted. If the effect does reach a certain level, the OPTIMIZER System will be implanted. The implant includes three electrical wires (leads) that connect the device to your heart through the veins inside your chest, very similar to procedures used when implanting a pacemaker device. The leads are used to record the normal electrical signals generated by your heart and to deliver the CCM treatment to your heart. The implantation is performed under sterile conditions with local anesthesia while you are awake, but possibly sedated. The implantation will be done either in an operating room or in a cardiac catheterization laboratory, depending upon the normal practices for implanting heart devices at your hospital.

Many patients with heart failure develop a need for a device called an implantable cardiac defibrillator (ICD) and/or a pacemaker. If you do not already have one of these devices, your doctor may recommend that one be implanted. If you are randomized to receive the OPTIMIZER System, the devices can be implanted at the same time. If you do have both devices, your doctor will perform tests to make sure that the devices do not interfere with each other. This could include a standard test used to confirm proper ICD function during which your heart is stimulated to beat abnormally (ventricular tachycardia or fibrillation).

Following a device implant you will have a chest X-ray before you are sent home. The OPTIMIZER System will be turned on for a brief period to make sure it is operating properly. During this time, you may also be instructed in how to use the battery charger. Before you leave the hospital, however, the OPTIMIZER System will be turned to sensing mode until your next visit to the doctor.

If you are randomized to the control group that does not receive the OPTIMIZER System you will continue to receive optimal medical therapy and you shall receive the same study related assessments as detailed below. If your doctor indicates that you have an indication for an ICD and/or pacemaker, this may be offered to you.

All patients will be asked to return to the hospital in two weeks after the beginning of the study. A physical examination and check of your medications will be performed. In subjects that have a pacemaker and/or ICD, that device will also be tested to make sure it is working properly. If you have received an OPTIMIZER implant, the device will be checked to make sure it is working properly and will be adjusted if necessary. The OPTIMIZER System will be turned ON to deliver the CCM treatment, which you will receive for the next 12 months. You will also receive instruction on when and how to use the battery charger, which you will take home with you. The OPTIMIZER System has a rechargeable battery, meaning that it can remain active for many years without having to be replaced. During normal use, the battery needs to be recharged every week for approximately 90 minutes. The energy for recharging is delivered through your skin by a device that you position over your collar bone. No wires or needles are required for this process.

All patients, including those in which the OPTIMIZER device was unable to be implanted, will be asked to return for follow-up visits at Weeks 4, 12, 24, 36 and 50 following your study start date. At every visit you will undergo medication review, medical history, physical examination and device interrogation. At weeks 12, 24 and 50 you will also be asked to complete the questionnaires about symptoms you have during your daily life, to undergo stress tests to see how much you can exercise (the 6 minute walk and the cardiopulmonary stress test) and to undergo an echocardiogram to check the strength of your heart. At weeks 12 and 24, the Holter monitor tests will be repeated to check the rate of your heart beat. As noted above, female patients of child bearing potential who received an OPTIMIZER System shall be asked to have a pregnancy test at weeks 24 and 50.

At the end of one year (50 weeks), if you have the OPTIMIZER System, you will have the option of continuing to receive CCM treatment if you and your doctor believe that it's the best choice for you. In such case, a medical history, medication review, physical examination and device interrogation will be performed at 3-month intervals until the FDA has completed its review of this study.

Foreseeable Risks Associated with Study Participation for Patients with the OPTIMIZER System

1. Risks associated with temporary placement of a catheter in your heart

Your doctor will temporarily place a catheter inside the main pumping chamber of your heart (left ventricle) through a small incision in an artery in your groin. This catheter will be used to measure the effects of the CCM treatment on your heart. The risks associated with temporary placement of this catheter include:

- infection
- bleeding
- irregular heartbeats (ventricular arrhythmias)
- damage to the heart or blood vessels
- death

2. Risks Associated with the OPTIMIZER System Implant and CCM Treatment

The risks associated with implantation of the OPTIMIZER System (which includes implantation of the pulse generator and the leads that connect the generator to your heart) and application of CCM treatment include:

- injury to the heart or blood vessels
- bleeding
- irregular heartbeats (arrhythmias, including abnormally slow or fast heart beats)
- damage to the heart muscle
- damage to specialized tissue in the heart responsible for initiating each heart beat (i.e., the heart's c*onduction system*)
- formation of blood clots
- stroke
- chest wall sensations
- pain at the incision site
- infection
- collapsed lung
- perforation of the leads through the heart wall
- lead dislodgement
- fluid or blood accumulation around the heart
- death

3. Risks Associated with the Use of Local Anesthesia

Risks associated with the use of local anesthesia used during the OPTIMIZER System implantation procedure are as follows:

- puncture of a vein
- localized pain at or around injection site
- numbness at or around injection site
- bruising

4. Risks associated with possible ICD and/or pacemaker device interactions

If you have an ICD, it is possible that the CCM pulses delivered by the OPTIMIZER System could be sensed and falsely interpreted by the ICD as a fast heart beat (ventricular tachycardia). If this should happen, the ICD may send an unnecessary shock to your heart. Studies in animals have not found this to be a problem when the ICD and the OPTIMIZER System are programmed correctly. Also, it cannot be excluded that the Optimizer III will cause the ICD to fail to deliver treatment for a life threatening arrhythmia. However, the Optimizer device is designed to minimize this possibility and prior testing and experience in patients confirm the unlikeliness of this occurring. Additionally, all personnel involved with programming the OPTIMIZER System have been trained on device programming and device interaction testing.

If you have a cardiac pacemaker it is possible that the CCM pulses delivered by the OPTIMIZER System could be sensed and falsely interpreted by the pacemaker as a regular heart beat. If this should happen, the pacemaker might not send pacing signals to your heart at a rate needed by your body, and could result in an abnormally slow or unsteady heart rhythm (bradycardia). Symptoms of bradycardia result from a lack of oxygen enriched blood being delivered to your body and include dizziness, fainting, extreme fatigue and shortness of breath.

Many of the risks associated with the implantation of the OPTIMIZER System are minimized by having trained and experienced physicians perform the implantation procedure, through the use of meticulous care during the implantation procedure and by having experienced physicians involved in your care throughout the study period.

5. Risk of an Optimizer System Surgical Revision

There is a potential that any system component could malfunction, become damaged, infected, or, in the case of the leads, become dislodged. System component malfunction or other clinical circumstances (e.g., sepsis) may require noninvasive corrective actions or possibly even a surgical revision (repositioning, replacement, or removal) of the malfunctioning component(s).

6. Unknown Risks

Because the OPTIMZER System is an experimental device, the application of CCM treatment to your heart may involve risks that are currently unknown. If you receive the OPTIMIZER System, you will be notified of any additional risks that become known during the study that may affect your decision of whether to continue in the study.

Foreseeable Risks Associated with Study Participation for All Study Patients

There is a risk for all patients enrolled in this study, whether you receive an OPTIMIZER System or not, that your heart failure signs and symptoms may become worse. Heart failure signs and symptoms include:

- Stroke or transient ischemic attacks (TIA)
- heart attack
- dizziness or lightheadedness
- palpitations
- increased fatigue/weakness
- shortness of breath or difficulty breathing
- fluid retention in the lungs
- severe swelling of the legs, feet and ankles
- abnormal heart rhythms (too fast or too slow)

There is also a risk of death associated with many of the signs and symptoms listed above.

Reasonably Expected Benefits to You and to Others

Your heart failure symptoms may improve as a result of receiving CCM treatment and this may help you exercise more or feel better. The study will determine the degree to which these benefits occur. However, because the therapy is not yet proven to be effective, you may not benefit from this study.

Appropriate Alternative Procedures or Treatments

Before offering you participation in this study, your doctor has made sure that you are already receiving the best possible medications for treating heart failure. Your doctor may discuss other treatment options, such as giving you a drug continuously into a vein to increase the strength of your heart (known as positive inotropic agents) or cardiac resynchronization therapy (another pacemaker like device for treating heart failure patients with certain types of cardiac conduction abnormalities). Therefore, the alternative to participating in this study is to choose not to participate and continue with your current medications or consider one of these other treatments.

Confidentiality

For the purpose of this study, your health data will be recorded and reviewed by the sponsor of the study (Impulse Dynamics) and by the US Food and Drug Administration (FDA) for evaluation. Representatives of the sponsor and the US FDA will inspect your health data. Any data that may be published in scientific journals will not reveal the identity of the study participants. Any information that is obtained in connection with this study that can be identified with you will remain confidential.

Compensation and Cost

The study sponsor will compensate you for your participation in this study according to the schedule listed below:

2-week follow-up visit:	$40
4-week follow-up visit:	$50
12-week follow-up visit:	$100
24-week follow-up visit:	$100
36-week follow-up visit:	$50
50-week follow-up visit:	$250

You will receive a single payment in one check that includes compensation for each visit that you completed. You will be given that payment after the 50-week follow-up visit. If you terminate your participation in the study prior to the 50-week visit, you will still receive a single payment for each visit that you completed. In addition, you may also be compensated for your transportation costs to and from the facility and your home (for travel over 75 miles), parking, meals and reasonable lodging (for travel over 75 miles). Mileage will be reimbursed at the standard rate of $0.36 per mile, which includes the cost of gasoline. You will be asked to maintain and submit receipts for reimbursement.

The study sponsor will be responsible for covering the research specific costs associated with your care. In some cases, insurance companies may continue to pay for routine procedures and services that you would typically incur whether or not you would be participating in the trial. A routine procedure or service is one that your doctor would have prescribed for you even if you were not in the clinical trial. In these cases, your insurer will be billed for these services. You will be responsible for paying any copayments and deductibles that you would normally be expected to pay.

Some insurers will cover some of the research related procedures and services. An example of a research related cost is the device, if you are in the group that receives the OPTIMIZER System. In these cases, you may be responsible for copayments and deductibles that you would ordinarily be expected to pay. Importantly, however, if you are required to have a procedure or service that is related to the clinical trial and is not reimbursed by your insurer, the study sponsor will cover the cost and you will not incur the cost for that procedure or service.

Injury

If you believe that you have suffered injury or damage to your health due to your participation in this study, it is necessary to immediately inform the Principal Investigator, Dr._____. Reasonable and necessary medical expenses incurred by you as a direct result of the treatment of an injury resulting from the OPTIMIZER System, the implant procedure or other procedures required by this study (other than standard of care procedures) and administered in accordance with the study protocol will be paid by the Study Sponsor to the extent such expenses are not

subject to your medical coverage and are not caused by the negligence or willful wrongdoing of the Hospital.

Contacts

Your doctor, will answer any of your questions about this study or about your rights as a research participants. If at any time you have any problems or questions regarding this study, please contact the following doctor: _____, MD at telephone:_____.

Voluntary Participation

Your participation in this study is voluntary. You may refuse to participate in this study or discontinue your participation at any time without any penalty or loss of benefits. Your decision will not influence the standard medical treatment you receive for your heart failure. If you received the OPTIMIZER System, and you choose to withdraw from the study, your doctor will ask you to return the battery recharger and the CCM therapy will be stopped.

Consent

I have carefully read the above information. I have asked any questions that I may have concerning the study and the experimental CCM treatment and I have been given a copy of this consent form for my records. By signing this form, I agree to participate in the study and to allow a representative of the sponsor and of the US FDA to inspect my health data.

Printed Name of Participant	
Signature of Participant	**Date**
Investigator Signature	**Date**
Legally Authorized Representative (if applicable)	**Date**

HIPAA Clinical Research Authorization

AUTHORIZATION TO USE AND DISCLOSE HEALTH INFORMATION

[*name of study*]

I agree to permit [*hospital*], my doctors, and my other health care providers (together "Providers"), and [*name of investigator(s)*] and [*his/her/their/its*] staff (together "Researchers"), to use and disclose health information about me as described below.

1. **The health information that may be used and disclosed includes:**
   - all information collected during the research described in the Informed Consent Form for the [*name of study*] ("the Research"); and
   - health information in my medical records that is relevant to the Research.

2. **The Providers may disclose health information in my medical records to:**
   - the Researchers;
   - the sponsor of the Research, IMPULSE DYNAMICS, and its agents and contractors (together "Sponsor"); and
   - representatives of government agencies, review boards, and other persons who watch over the safety, effectiveness, and conduct of research.

3. **The Researchers may use and share my health information:**
   - among themselves and with other participating researchers to conduct the Research; and
   - as permitted by the Informed Consent Form.

4. **The Sponsor may use and share my health information as permitted by the Informed Consent** Form.

5. **Once my health information has been disclosed to a third party,** federal privacy laws may no longer protect it from further disclosure.

6. Please note that:

- You do not have to sign this Authorization, but if you do not, you may not participate in the Research.
- You may change your mind and revoke (take back) this Authorization at any time and for any reason. To revoke this Authorization, you must write to _____. However, if you revoke this Authorization, you will not be allowed to continue taking part in the Research. Also, even if you revoke this Authorization, the Researchers and the Sponsor may continue to use and disclose the information they have already collected as permitted by the Informed Consent Form.
- **[*Note—Include this bullet point only if the IRB determines that suspension of participants' access to information is appropriate*.]** While the Research is in progress, you will not be allowed to see your health information that is created or collected by the [*Hospital entity*] in the course of the Research. After the Research is finished, however, you may see this information as described in [*Hospital entity*]'s Notice of Privacy Practices.

7. This Authorization does not have an expiration (ending) date.

8. You will be given a copy of this Authorization after you have signed it.

_____	_____
Signature of participant or participant's legal representative	Date
_____	_____
Printed name of participant or participant's legal representative	Representative's relationship to participant

APPENDIX C

TEMPLATE CASE REPORT FORMS

Data for this study will actually be recorded into data entry screens using the Medidata electronic data capture system. Template case report forms are available on disk for reference use only. Due to the extensive use of drop-down options available on each form, the printed version is over 500 pages. The following is a list of the electronic Case Report Forms available on Medidata:

Screening Visit Forms:
- Demographics
- Medical History
- Baseline Medications
- Baseline Physical Examination

Baseline Visit Forms:
- Pregnancy Test
- NYHA Classification
- NYHA Questionnaire
- Minnesota Living with Heart Failure Questionnaire
- Echocardiogram
- 6 Minute Walk Test
- Cardiopulmonary Stress Test
- 12-Lead ECG
- 24 Hour Holter Monitor
- Eligibility Determination
- Randomization
- Health Insurance Coverage

Implant Folder (for Subjects Randomized to the Optimizer System):
- Follow Up Medications
- Follow-up Physical Examination
- Implant Success
- Implant- PSA Measurements
- Implant- dP/dt Evaluation
- Implant- Optimizer and Lead Information
- Implant- Equipment Notes, & Personnel
- Discharge
- Optimizer Interrogation

Follow-up Folders:

- Interim Medical History
- Follow Up Medications
- Follow-Up Physical Examination
- NYHA Classification
- NYHA Questionnaire
- Minnesota Living with Heart Failure Questionnaire
- Echocardiogram
- 6 Minute Walk Test
- Cardiopulmonary Stress Test
- 24 Hour Holter Monitor
- Health Insurance Coverage
- Optimizer Interrogation (for subjects randomized to the Optimizer System)
- VT-VF Episodes
- Pregnancy Test

Miscellaneous Forms

- ICD System/ Pacemaker
- Concomitant Device Interaction Testing
- End of Study/Withdrawal
- Patient Correspondence Log
- Protocol Deviation
- Adverse Event Log
- Adverse Event Forms
- Optimizer System Device Malfunction Log
- Hospitalization Log
- Procedure Log
- Mortality Form

APPENDIX D

TREATMENT OF SUBJECTS ENROLLED IN PHASE I OF THE FIX-HF-5 STUDY

Background

On May 6, 2004, FDA conditionally approved the Evaluation of the Safety and Efficacy of the OPTIMIZER™ II System with Active Fixation Leads in Subjects with Heart Failure Resulting from Systolic Dysfunction: FIX-HF-5. The evaluation was designed as a prospective, double-blind, multi-center study of subjects with moderate to severe heart failure. An interim safety evaluation was planned after completion of the first 50 implants (Phase I), with a DSMB decision required before proceeding with additional patient enrollment (Phase II). All Phase I patients received an OPTIMIZER™ II System and were randomized to either have the device either turned "ON" or "OFF" for the first six months of follow-up. Patients were informed that if their device was turned "ON" for the first six months, the battery would deplete and the device would need to be replaced. If their device was turned "OFF" for the first six months, it would be turned "ON" after they completed the first six months of follow-up.

Changes are now proposed to the study design and to the device. The new generation of the device, the OPTIMIZER™ III System is now being introduced; this device has a rechargeable battery meaning that it does not have to be replaced after every 6 month period. Because of this, however, the study design is now extending to two groups (treatment versus control) that are followed for twelve (12) instead of six (6) months. The study will transition into an un-blinded safety and effectiveness evaluation of patients who will either receive or not receive the OPTIMIZER™ III System. This appendix is intended for those centers that enrolled patients into Phase I of the IDE study, and describes the methods used for the ongoing evaluation of those subjects.

The sequence and duration of these follow-up intervals are described in **Table 1**.

Study Procedures

The main changes to the original protocol (May 6, 2004) in which 50 Phase I study subjects are participating shall be:

1. At the point of OPTIMIZER II battery depletion, all subjects shall be offered the opportunity to have a device replacement with an OPTIMIZER™ III pulse generator as a replacement device. For subjects randomized to "ON" during the first 6 months, this replacement is expected to occur following completion of the first 6 months of the study. For subjects randomized to "OFF" during the first 6 months, this replacement is expected to occur following completion of the second 6 month period. The decision of whether or not to perform the replacement shall be made by the patient in consultation with the Principal Investigator and shall be based upon their clinical decision as to whether or not the patient appeared to have benefited from the treatment.
2. In addition to the tests specified in the original protocol, Phase I subjects shall be asked to undergo a cardiopulmonary stress test (CPX), an echocardiogram and a 6 minute hall walk test (6MW) at the 50 week follow-up visit.
3. The expected duration of subject participation shall not change from the originally indicated 13 months (including the screening, baseline, and 12 months of follow-up). However, subjects who choose to have an OPTIMIZER™ III pulse generator implant shall be asked to return for routine follow-up and generator checks at 3 month intervals for as long as long as they choose to have the device in place and choose to keep it active until the FDA completes their review of this study.

The subjects enrolled in Phase I of the study shall be informed of the changes to the protocol since they originally agreed to participate and shall be asked to sign an informed consent document that describes the risks and potential benefits of the changes. The risks include those associated with performing the additional tests described above (CPX, 6MW and an echocardiogram). The risks associated with these test are considered to be minimal and clinically acceptable, as detailed in the original study. Participation shall be voluntary. Any subject not wishing to participate is free to withdraw from the study.

OPTIMIZER II => III Device Replacement

The OPTIMIZER II pulse generator will be replaced with the OPTIMIZER™ III rechargeable pulse generator, which is connected to the three leads placed during the initial implant procedure. The device replacement procedure is performed under sterile technique. Device interaction (if the patient has an ICD) and function is checked and a chest X-ray taken according to hospital policy to evaluate lead placement. Patients may be instructed on when and how to use the battery charger and will be discharged with the device turned on.

Patients will be asked to return to the hospital two weeks after the device replacement for a physical examination, a medication check, and device interrogation. Additional instruction on use of the battery charger will be provided as necessary.

Post Study Follow-Up

Following the 50 week follow up, subjects can continue to receive treatment with CCM signals. These patients shall be seen at ~6 month intervals at the investigational site. These follow-up visits shall include an Optimizer device interrogation and reporting of any Optimizer device-related serious adverse events (and the corresponding hospitalizations and procedures, if any) and all deaths. These visits shall continue until FDA has made a determination of device safety and efficacy. In the event that the study is terminated prior to approval, the device is found to be ineffective or at the request of the patient, the device can be removed. Alternatively, the device can be left in place and deactivated; in this case, the device charger would be retrieved from the patient in order to eliminate the possibility of further use of the device.

Consent Materials

A template consent for the Phase I Patients requesting a device exchange is attached.

A consent addendum is included in Appendix F to inform subjects with the OPTIMIZER III System of the modified follow-up requirements and the availability of the OPTIMIZER IVs System.

TABLE 1. Schedule of Events										Post-Randomization					
TEST	**Screening**	**Baseline**	**Implant**	**Week 2[§] ±2days**	**Week 4[‡] ±2days**	**+4 ±1 wks**	**+12±1 wks**	**+22±1 wks**	**+24±1 wks**	**Device Exchange[†]**	**+2 wks ±2days[†]**	**36±2 wks**	**50±2 wks**	**Device Exchange[††]**	**Every 6 Months ****
Informed consent	X									X*				X*	
Medical History	X			X	X	X	X		X		X	X	X		X
Physical Examination	X		X	X	X	X	X		X		X	X	X		
Medications	X		X	X	X	X	X		X		X	X	X		
NYHA Classification	X					X	X		X			X	X		
Echocardiogram		X					X		X				X		
MLWHFQ		X				X	X		X			X	X		
6-minute walk		X				X	X		X				X		
Cardiopulmonary Stress Test		X					X		X				X		
24 hour Holter Monitor		X				X	X		X						
Urine pregnancy test		X							X				X		
Eligibility determination		X													
OPTIMIZER™ II System Implant			X												
Chest X-ray			X												
In-Hospital System Activation			X							X				X	
Device Interrogation / Programming			X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization				X[§]	X[‡]										
OPTIMIZER™ Device Exchange										X[†]				X[††]	
Adverse Events, Hospitalizations, Procedures (as needed) /OPTIMZER device-related SAEs after 50-wks		X	X	X	X	X	X	X	X	X	X	X	X	X	X

NOTE: Subjects withdrawn due to an unsuccessful implant procedure (includes cases that failed to achieve ≥5% increase in dP/dtmax during acute CCM signal application) should be evaluated again between 2 and 4 weeks after the procedure and report any post-procedural adverse events as needed.

* Phase 2 informed consent required one time prior to device exchange at 24 weeks to receive the Optimizer III System or the 50-week interval.

§ All subjects will undergo a visit 2 weeks after device implantation. "Single" implant subjects will be randomized and device activated according to group assignment.

‡ Dual implant subjects (i.e., those who underwent ICD/pacemaker implant at the same time as OPTIMIZER™ II implant) will undergo a second post-implantation visit 4 weeks after device implantation at which point the device will be activated according to group assignment.

† For subjects randomized to have the OPTIMIZER II device "ON" for the first 6 months, the device will reach end-of-battery life on average at 26-weeks and shall be offered the OPTIMIZER III pulse generator at that point. Patients will be seen 2 weeks after their device exchange procedure.

†† For subjects randomized to have the OPTIMIZER II device "OFF" for the first 6 months and then "ON" for the second 6 month period, the device will reach end-of-battery life on average at 52-weeks and shall be offered the OPTIMIZER III pulse generator at that point. Patients will be seen 2 weeks after their device exchange procedure.

** Patients receiving the OPTIMIZER III device will be followed every six months following the 50-week interval for as long as they have the device in place and choose to keep it active, until either the study is terminated or the FDA completes their review of this study. Patients with a depleted OPTIMIZER II System battery who choose not to receive the OPTIMIZER III pulse generator have met the protocol follow-up requirements after the 50-week visit and may be discontinued from the study. Follow-up window is +/- 4 weeks.

Subject ID Number:___-_____

Evaluation of the Safety and Efficacy of the
OPTIMIZER™ System with Active Fixation Leads in
Subjects with Heart Failure Resulting from Systolic Dysfunction:
FIX-HF-5

INFORMED CONSENT

Introduction

Several months ago you signed an informed consent document and were enrolled in a research study for the OPTIMIZER™ II System (an experimental medical device). The OPTIMIZER™ II System battery has now depleted and in order to continue CCM treatment, the portion of the device that contains the battery needs to be replaced.

You are now being asked to consider continuing your voluntary participation in this research study, which is being sponsored by a company called IMPULSE DYNAMICS (USA), Inc. Please read the following information carefully and discuss any questions you have with your doctor.

Expected Duration of Study Participation

Your participation in this study is expected to be an additional 6 months (for those subject randomized to have CCM treatment ON for the first six months of the study), with additional follow-up every 3 months for as long as you have the device in place and choose to keep it active until the FDA completes their review of this study. This follow up may take up to 5 years.

Study Procedures

The battery in the OPTIMIZER™ II System that you had implanted several months ago has now depleted. The study sponsor has modified that version of the device to one that is now rechargeable, called the OPTIMIZER™ III System. The replacement device (OPTIMIZER™ III) will be connected to the three electrical wires (leads) that were already implanted in your heart when you received the OPTIMIZER™ II System. The device replacement procedure is performed under sterile conditions with local anesthesia while you are awake. The implantation will be done either in an operating room or in a cardiac catheterization laboratory, depending upon the normal practices for implanting heart devices at your hospital.

After the OPTIMIZER™ III device is implanted, your doctor will perform tests to make sure that it is functioning properly. If you have an ICD (defibrillator) and/or pacemaker in your heart, your doctor will also do a test to verify that the devices are not interfere with each other's function. You will have a chest X-ray taken to verify that the leads in your heart are still optimally placed. Before you leave the hospital, the OPTIMIZER III System will be turned on to deliver the CCM treatment, which you will receive for as long as you choose to keep the device charged. You will be instructed on how to use the battery charger, which you will take home with you. The OPTIMIZER III System has a rechargable battery, meaning that it can remain active for many years without having to be replaced. During normal use, the battery needs to be recharged every week for approximately 90 minutes. The energy for recharging is delivered through your skin by a device that you position over your collar bone. No wires or needles are required for this process. Your doctor will continue to follow you closely to ensure that you charging the device appropriately and are receiving optimal medical therapy for your heart failure condition.

You will be asked to return to the hospital in two weeks after the device replacement for a physical examination and a check of your medications. If you have a pacemaker and/or ICD, that device as well as the OPTIMIZER III System will be tested to make sure they are working properly and adjusted if necessary.

If you have not done so already, you will be asked to return for follow-up visits at Weeks 36 and 50 following the date of your initial OPTIMIZER II System implant. During these two visits you will undergo medication review, medical history, physical examination and device

interrogation. At week 50 you will also be asked to complete the two questionnaires about symptoms you have during your daily life, to undergo stress tests to see how much you can exercise (the 6 minute walk and the cardiopulmonary stress test) and to undergo an echocardiogram to check the strength of your heart.

At the end of one year (~50 weeks) or after receiving the OPTIMIZER III System (whichever comes last), you will have the option of continuing to receive CCM treatment if you and your doctor believe that it's the best choice for you. In such case, you will continue to be followed at approximately 3 month intervals until the FDA has completed its review of this study.

Foreseeable Risks Associated with the OPTIMIZER System

1. Risks Associated with replacement of the OPTIMIZER System and CCM Treatment

The risks associated with replacement of the OPTIMIZER System and application of CCM treatment include:

- bleeding
- pain at the incision site
- infection

2. Risks Associated with the OPTIMIZER System Implant and CCM Treatment

The risks associated with implantation of the OPTIMIZER System (which includes implantation of the pulse generator and the leads that connect the generator to your heart) and application of CCM treatment include:

- injury to the heart or blood vessels
- bleeding
- irregular heartbeats (arrhythmias, including abnormally slow or fast heart beats)
- damage to the heart muscle
- damage to specialized tissue in the heart responsible for initiating each heart beat (i.e., the heart's c*onduction system*)
- formation of blood clots
- stroke
- chest wall sensations
- pain at the incision site
- infection
- collapsed lung

- perforation of the leads through the heart wall
- lead dislodgement
- fluid or blood accumulation around the heart
- death

3. Risks Associated with the Use of Local Anesthesia

Risks associated with the use of local anesthesia used during the OPTIMIZER System replacement procedure are as follows:

- puncture of a vein
- localized pain at or around injection site
- numbness at or around injection site
- bruising

4. Risks associated with ICD/pacemaker device interaction

If you have an ICD, it is possible that the CCM pulses delivered by the OPTIMIZER System could be sensed and falsely interpreted by the ICD as a fast heart beat (ventricular tachycardia). If this should happen, the ICD may send an unnecessary shock to your heart. Studies conducted in animals indicate that this should not occur when the appropriate type of ICD lead is used and when the ICD and the OPTIMIZER System are programmed correctly.

If you have a pacemaker that is set for pacing your heart beat, it is possible that the CCM pulses delivered by the OPTIMIZER System could be sensed and falsely interpreted by the pacemaker as a regular heart beat. If this should happen, the pacemaker might not send pacing signals to your heart at a rate needed by your body, and could result in an abnormally slow or unsteady heart rhythm (bradycardia). Symptoms of bradycardia result from a lack of oxygen enriched blood being delivered to your body and include dizziness, fainting, extreme fatigue and shortness of breath.

Many of the risks associated with the replacement of the OPTIMIZER System are minimized by having trained and experienced physicians perform the implantation procedure, through the use of meticulous care during the replacement procedure and by having experienced physicians involved in your care throughout the study period. Also, it cannot be excluded that the Optimizer III will cause the ICD to fail to deliver treatment for a life threatening arrhythmia. However, the Optimizer device is designed to eliminate this possibility and prior

testing and experience in patients confirm the unlikeliness of this occurring. Additionally, all personnel involved with programming the OPTIMIZER System have been trained on device programming and device interaction testing.

5. Risks Associated with Heart Failure

There is a risk for all patients enrolled in this study that your heart failure signs and symptoms may become worse. Heart failure signs and symptoms include:

- stroke
- heart attack
- dizziness or lightheadedness
- palpitations
- increased fatigue/weakness
- shortness of breath or difficulty breathing
- fluid retention in the lungs
- severe swelling of the legs, feet and ankles
- abnormal heart rhythms (too fast or too slow)

There is also a risk of death associated with many of the signs and symptoms listed above.

6. Risk of an Optimizer System Surgical Revision

There is a potential that any system component could malfunction, become damaged, infected, or, in the case of the leads, become dislodged. System component malfunction or other clinical circumstances (e.g., sepsis) may require noninvasive corrective actions or possibly even a surgical revision (repositioning, replacement, or removal) of the malfunctioning component(s).

7. Unknown Risks

Because the OPTIMZER System is an experimental device, the application of CCM treatment to your heart may involve risks that are currently unknown. You will be notified of any additional risks that become known during the study that may affect your decision of whether to continue in the study.

Reasonably Expected Benefits to You and to Others

Your heart failure symptoms may improve as a result of receiving CCM treatment and this may help you exercise more or feel better. The study will determine the degree to which these benefits occur. However, because the therapy is not yet proven to be effective, you may not benefit from this study.

Alternative Procedures or Treatments

As a participant in this study, your doctor is making sure that you are receiving the best possible medications for treating heart failure. Your doctor may discuss other treatment options, such as giving you a drug continuously into a vein to increase the strength of your heart (known as positive inotropic agents) or cardiac resynchronization therapy (another pacemaker like device for treating heart failure patients with certain types of cardiac conduction abnormalities). Therefore, the alternative to continuing your participation in this study is to choose not participate (and not to receive a replacement OPTIMIZER System) and continue with your current medications or consider one of the other treatments mentioned above.

Confidentiality

For the purpose of this study, your health data will be recorded and reviewed by the sponsor of the study (Impulse Dynamics) and by the US Food and Drug Administration (FDA) for evaluation. Representatives of the sponsor and the US FDA will inspect your health data. Any data that may be published in scientific journals will not reveal the identity of the study participants. Any information that is obtained in connection with this study that can be identified with you will remain confidential.

Compensation and Cost

You will not be compensated for your participation in this study but you may be reimbursed for the following costs you may incur as a study participant:

- Transportation costs to and from the facility and your home (for travel over 75 miles). Mileage will be reimbursed at the standard rate of $0.36 per mile (or current standard rate), which includes the cost of gasoline.
- Parking
- Meals and reasonable lodging (for travel over 75 miles)

NOTE: You will be asked to maintain and submit receipts for reimbursement.

The study sponsor will be responsible for covering the research specific costs associated with your care. In some cases, insurance companies may continue to pay for routine procedures and services that you would typically incur whether or not you would be participating in the trial. A routine procedure or service is one that your doctor would have prescribed for you even if you were not in the clinical trial. In these cases, your insurer will be billed for these services. You will be responsible for paying any copayments and deductibles that you would normally be expected to pay.

Some insurers will cover some of the research related costs (such as the cost of the OPTIMIZER System), procedures and services. In these cases, you may be responsible for copayments and deductibles that you would ordinarily be expected to pay. Importantly, however, if you are required to have a procedure or service that is related to the clinical trial and is not reimbursed by your insurer, the study sponsor will cover the cost and you will not incur the cost for that procedure or service.

Injury

If you believe that you have suffered injury or damage to your health due to your participation in this study, it is necessary to immediately inform the Principal Investigator, Dr._____. Reasonable and necessary medical expenses incurred by you as a direct result of the treatment of an injury resulting from the OPTIMIZER System, the implant procedure or other procedures required by this study (other than standard of care procedures) and administered in accordance with the study protocol will be paid by the Study Sponsor to the extent such expenses are not subject to your medical coverage and are not caused by the negligence or willful wrongdoing of the Hospital.

Contacts

Your doctor, will answer any of your questions about this study or about your rights as a research participants. If at any time you have any problems or questions regarding this study, please contact the following doctor: _____, MD at telephone:_____.

Voluntary Participation

Your participation in this study is voluntary. You may refuse to participate in this study or discontinue your participation at any time without any penalty or loss of benefits. Your decision will not influence the standard medical treatment you receive for your heart failure. If you choose to withdraw from the study, your doctor will ask you to return the battery recharger and the CCM therapy will be stopped.

Consent

I have carefully read the above information. I have asked any questions that I may have concerning the study and the experimental CCM treatment and I have been given a copy of this consent form for my records. By signing this form, I agree to continue my participation in the study and to allow a representative of the sponsor and of the US FDA to inspect my health data.

Printed Name of Participant	
Signature of Participant	**Date**
Investigator Signature	**Date**
Legally Authorized Representative (if applicable)	**Date**

HIPAA Clinical Research Authorization

AUTHORIZATION TO USE AND DISCLOSE HEALTH INFORMATION

[*name of study*]

I agree to permit [*hospital*], my doctors, and my other health care providers (together "Providers"), and [*name of investigator(s)*] and [*his/her/their/its*] staff (together "Researchers"), to use and disclose health information about me as described below.

1. **The health information that may be used and disclosed includes:**
   - all information collected during the research described in the Informed Consent Form for the [*name of study*] ("the Research"); and
   - health information in my medical records that is relevant to the Research.

2. **The Providers may disclose health information in my medical records to:**
   - the Researchers;
   - the sponsor of the Research, IMPULSE DYNAMICS, and its agents and contractors (together "Sponsor"); and
   - representatives of government agencies, review boards, and other persons who watch over the safety, effectiveness, and conduct of research.

3. **The Researchers may use and share my health information:**
   - among themselves and with other participating researchers to conduct the Research; and
   - as permitted by the Informed Consent Form.

4. **The Sponsor may** use and share my health information as permitted by the Informed Consent Form.

5. **Once my health information has been disclosed to a third party,** federal privacy laws may no longer protect it from further disclosure.

6. **Please note that:**
   - You do not have to sign this Authorization, but if you do not, you may not participate in the Research.
   - You may change your mind and revoke (take back) this Authorization at any time and for any reason. To revoke this Authorization, you must write to _____. However, if you revoke this Authorization, you will not be allowed to continue taking part in the Research. Also, even if you revoke this Authorization, the Researchers and the Sponsor may continue to use and disclose the information they have already collected as permitted by the Informed Consent Form.
   - **[*Note—Include this bullet point only if the IRB determines that suspension of participants' access to information is appropriate.*]** While the Research is in progress, you will not be allowed to see your health information that is created or collected by the [*Hospital entity*] in the course of the Research. After the Research is finished, however, you may see this information as described in [*Hospital entity*]'s Notice of Privacy Practices.

7. **This Authorization does not have an expiration (ending) date.**

8. **You will be given a copy of this Authorization after you have signed it.**

_____	_____
Signature of participant or participant's legal representative	Date
_____	_____
Printed name of participant or participant's legal representative	Representative's relationship to participant

APPENDIX E

Device-device Interaction Testing Procedure

Subjects that have a concomitant device (e.g., ICD, pacemaker) will undergo additional testing at the end of the implant procedure to ensure appropriate function of both the Optimizer III and the concomitant device. The following steps summarize the required testing:

1. Program the sensing windows of the Optimizer and ensure that the Optimizer III can be programmed to consistently delivery CCM therapy in the presence of the concomitant device.
2. Activate CCM therapy and evaluate the real-time intracardiac electrograms and marker channels to ensure that CCM therapy does not cause inappropriate oversensing during normal sinus rhythm that cannot be resolved through reprogramming or lead repositioning.
3. Activate CCM therapy and evaluate the real-time intracardiac electrograms and marker channels to ensure that CCM therapy does not cause inappropriate undersensing during normal sinus rhythm that cannot be resolved through reprogramming or lead repositioning.
4. While CCM therapy is being delivered, ensure that CCM therapy does not cause inappropriate inhibition of bradycardia pacing. In patients that require bradycardia pacing, activate CCM therapy during pacing and evaluate the real-time intracardiac electrograms and marker channels to ensure that CCM therapy does not cause inappropriate inhibition of bradycardia pacing therapy that cannot be resolved through reprogramming or lead repositioning.
5. Program the ICD to detect and convert an induced ventricular tachyarrhythmia. Program the Optimizer III to deliver continuous CCM therapy. While CCM therapy is being delivered, induce VT/VF and ensure that the implanted ICD can appropriately detect the ventricular tachyarrhythmia. Ensure that CCM therapy does not cause inappropriate undersensing during VT/VF that cannot be resolved through reprogramming or lead repositioning.

Appendix F
OPTIMIZER III Long-term Follow-up

Background

The FIX-HF-5 study included a Phase I and Phase II, with all active study subjects currently implanted with the OPTIMIZER™ III System. This appendix is intended for those centers that enrolled patients into the FIX-HF-5 study with subjects who currently have the Optimizer III System implanted and are being seen for follow-up every 3 months. The OPTIMIZER III IPG is no longer being manufactured the Sponsor. The Sponsor believes subjects should have the option to receive the current generation IPG, the OPTIMIZER IVs.

Study Follow-Up

The requirement to bring subjects back for a follow-up visit every 3 months is no longer consistent with current practice regarding other electrophysiology devices, including those that are life-saving devices. Additionally, in markets where the Optimizer System is market approved, follow-up visits after the initial acute follow-up phase are only required on an as needed basis when the patient receives a message on their device during a charging session or are unable to charge the device. To reduce the burden on the patient, the research institution and the Sponsor, the follow-up frequency is being extended to every 6 months.

Device Replacement

Another protocol called the FIX-HF-5C Confirmatory Study protocol is being conducted under the same IDE as the FIX-HF-5 Study. Subjects in the FIX-HF-5C Study will receive the new generation device, the OPTIMIZER™ IVs System. The OPTIMIZER IVs is very similar in its design to the OPTIMIZER III System with regard to its intended use, safety, performance, and design characteristics. The Optimizer IVs System employs the same atrial and ventricular leads as Optimizer III System. The purpose of the OPTIMIZER IVs is to offer patients a smaller and thinner IPG with a smaller and more portable charger. The OPTIMIZER III IPG is no longer being manufactured by Impulse Dynamics, so if IPG replacement becomes necessary, subjects will be provided the OPTIMIZER IVs System at that time. Subjects who do not wish to have the newer OPTIMIZER IVs implanted will have the OPTIMIZER III IPG de-activated and if they wish, the device may be explanted.

IRB Approval

OPTIMIZER III IPG replacement with the OPTIMIZER™ IVs pulse generator will only be performed at centers with IRB approval of the FIX-HF-5C Confirmatory Study, which includes the OPTIMIZER IVs Patient Manual and OPTIMIZER IVs Physician Manual.

Any FIX-HF-5 Study Investigator not participating in the FIX-HF-5C Study that wishes to use an OPTIMIZER IVs IPG for a revision/replacement procedure must request an "Approved Deviation From Protocol" from their IRB, the Sponsor and the FDA.

Consent Materials

A template informed consent addendum is attached for all subjects currently active in the FIX-HF-5 protocol.

Informed Consent Addendum for Participation in Research Activities
Impulse Dynamics FIX-HF-5 Optimizer Study

Dear Optimizer Study Research Participant:

You are currently taking part in the above-named research study. Before beginning this research study, you signed an Informed Consent that fully described the study and your rights as a research participant. The purpose of this Informed Consent Addendum is to provide you with new information about the study. Though the initial phase of the research study is completed, minimal data continues to be collected at approximately 3-month intervals primarily to determine if your Optimizer device is functioning appropriately.

We are writing to inform you that routinely scheduled visits will now take place approximately every 6-months, unless your doctor decides more frequent visits are necessary. You should still contact and see your doctor whenever you have a problem with your device or you do not feel well. You are reminded to continue charging your OPTIMIZER device on a weekly basis. Failure to keep your device battery charged may cause permanent damage to the battery.

We also want to let you know that if you ever need the Optimizer device replaced, you will be offered the most current version of the device called the Optimizer IVs System, which is the next generation of the device you currently have. The Optimizer IVs device is very similar to your current device but is smaller and thinner and uses a smaller more portable charger. If you do not wish to have the newer OPTIMIZER IVs implanted, the OPTIMIZER III IPG will be turned off, if it hasn't been already, and if you wish, the device may be removed.

STATEMENT OF CONSENT:

I have read all of the new information in this addendum concerning the study I am currently participating in. I have been given the opportunity to discuss the information contained in this addendum. All of my questions have been answered to my satisfaction. I understand that all previous statements of informed consent that were contained in the original consent document that I signed are still applicable, including potential benefits and risks.

I give my informed and voluntary consent to continue as a participant in this study. A copy of this form will be given to me.

_____ _____

Signature of Research Participant Date

_____

Print Name of Research Participant

The Statistical Analysis Report for the FIX-HF-5 Clinical Study of the OPTIMIZER System in Patients with Medically Refractory Heart Failure

By

Richard P. Chiacchierini, Ph.D.

I. Introduction

Moderate to severe heart failure is associated with disability that significantly limits exercise tolerance and is associated with poor quality of life. The OPTIMIZER System delivers cardiac contractility modulation, non-excitatory signals during the myocardial absolute refractory period synchronized with locally sensed electrical activity, intended to improve symptoms in treated subjects.

The statistical analysis below provides a detailed description of the analyses conducted, hypotheses tested, the precise statistical methods used and the populations analyzed. The analysis methods provide a thorough evaluation of the OPTIMIZER System in the population of moderate to severe heart failure subjects.

II. Study Design

This is a multicenter, randomized, prospective, parallel group clinical trial to evaluate the safety and efficacy of the OPTIMIZER™ System with active fixation leads in subjects with moderate to severe heart failure. Four hundred and twenty eight (428) subjects from 50 centers in the US were randomized with equal probability to implantation of the OPTIMIZER™ System in combination with optimal medical treatment (OMT) for heart failure or to OMT alone. Randomization used permuted blocks of four and was stratified by center and etiology of heart failure (ischemic versus non-ischemic cardiomyopathy). The nature of the treatment and requirement for one-year follow up precluded blinding of subjects and their treating clinicians, however, safety data were adjudicated by an independent committee of physician experts according to pre-specified criteria.

III. Objective

The objective of this investigation was to evaluate the safety and effectiveness of the OPTIMIZER™ System with active fixation leads in subjects with moderate to severe heart failure.

IV. Study Sites and Patient Distribution

The distribution of patients by study site and treatment group is given in the table below.

Table IV. 1 Distribution of Patients by Treatment Group and Study Site

Site Number and Name	Consented	Control n (%)	Optimizer n (%)	Total Randomized
01 Lancaster General Hospital	17	2 (33.3)	4 (66.7)	6
02 Mayo Clinic	5	2 (66.7)	1 (33.3)	3
03 CVMG of S. California	19	5 (50.0)	5 (50.0)	10
04 Medical College of Virginia	3	1 (50.0)	1 (50.0)	2
05 St. Luke's - Roosevelt Hospital	4	1 (50.0)	1 (50.0)	2
06 Ohio State University	10	4 (57.1)	3 (42.9)	7
08 Stern Cardiovascular Center	14	3 (42.9)	4 (57.1)	7
09 Tyler CVC	53	13 (50.0)	13 (50.0)	26
10 Aurora Denver Cardiology	5	1 (33.3)	2 (66.7)	3
11 Hershey Medical Center	2	0 (0.0)	0 (0.0)	0
12 Beth Israel (Newark)	16	5 (50.0)	5 (50.0)	10
13 St. Joseph's Hospital	37	10 (52.6)	9 (47.4)	19
14 UAB	5	1 (50.0)	1 (50.0)	2
15 St. Luke's (Milwaukee)	18	6 (50.0)	6 (50.0)	12
16 UCSD Medical Center	2	0 (0.0)	0 (0.0)	0
17 Pacific Rim EP	28	8 (47.1)	9 (52.9)	17
18 Forsyth Medical Center	7	3 (60.0)	2 (40.0)	5
19 Deborah Heart & Lung Center	9	2 (40.0)	3 (60.0)	5
20 Heart Care Associates	32	9 (56.3)	7 (43.7)	16
21 Harper University Hospital	24	6 (66.7)	3 (33.3)	9
22 Texas Cardiac Arrhythmia	17	6 (54.5)	5 (45.5)	11
23 Baylor (Houston)	9	3 (42.9)	4 (57.1)	7
24 Overlake Hospital - Hope Heart Institute	3	2 (100.0)	0 (0.0)	2
25 St. Francis Hospital	10	2 (40.0)	3 (60.0)	5
26 UT Southwestern	35	11 (47.8)	12 (52.2)	23
27 Lone Star Arrhythmia	85	25 (50.0)	25 (50.0)	50
28 University of Florida (Tampa)	8	1 (33.3)	2 (66.7)	3
29 Henry Ford Hospital	9	1 (50.0)	1 (50.0)	2
30 Riverside Regional Medical Center	23	4 (50.0)	4 (50.0)	8
31 Midwest Heart Foundation	13	2 (40.0)	3 (60.0)	5
32 Ochsner	30	6 (42.9)	8 (57.1)	14
33 St. Paul Heart Clinic	16	4 (44.4)	5 (55.6)	9
34 LBCVRF at Moses Cone	3	0 (0.0)	1 (100.0)	1
35 Northwestern University	13	5 (55.6)	4 (44.4)	9
36 Inova Arrhythmia Associates	18	8 (57.1)	6 (42.9)	14
37 Mt. Sinai Hospital (Miami Beach)	22	7 (58.3)	5 (41.7)	12
38 Texsan Heart Hospital	6	1 (50.0)	1 (50.0)	2
39 Arizona Arrhythmia Consultants	10	2 (40.0)	3 (60.0)	5
40 Deaconess Medical Center	5	0 (0.0)	3 (100.0)	3
41 Bryan LGH Heart Institute	46	17 (50.0)	17 (50.0)	34

Table IV.1 Distribution of Patients by Treatment Group and Study Site (Continued)

Site Number and Name	Consented	Control n (%)	Optimizer n (%)	Total Randomized
42 Vanderbilt Univ. Medical Center	7	1 (25.0)	3 (75.0)	4
43 California Pacific Medical Center	8	3 (60.0)	2 (40.0)	5
44 Emory	15	4 (50.0)	4 (50.0)	8
45 NYU	5	1 (33.3)	2 (66.7)	3
46 Lahey Clinic	10	2 (33.3)	4 (66.7)	6
47 Cardiovascular Associates	5	1 (33.3)	2 (66.7)	3
48 University of Wisconsin Hospital	6	3 (100.0)	0 (0.0)	3
49 Presbyterian Medical Center	23	9 (56.3)	7 (43.7)	16
50 Scripps Clinic	4	0 (0.0)	0 (0.0)	0
Grand Totals	**774**	**213 (49.8)**	**215 (50.2)**	**428**

V. Patient Accountability

The accountability of patients with study visits is presented in the table below.

Table V.1 Patient Accountability and Follow-up

Interval	Week 2	Week 4	Week 12	Week 24	Week 36	Week 50
Control						
Enrolled	213	213	213	213	213	213
Died[1]	0	0	1	1	3	7
Withdrawn[1]	2[4]	4[4]	6[4]	8[4]	9[4]	22[4]
Intervention not Withdrawn[1]	0	0	0	1	1	4
Eligible[2]	211	209	206	203	199	181
Visit in Window	155	179	173	166	165	143
Visit Outside Window	31	18	18	23	19	34
No Visit	25	12	15	14	15	3
Optimizer						
Enrolled	215	215	215	215	215	215
Died[1]	1	1	7[3]	10[3]	12[3]	13[3]
Withdrawn[1]	3[4]	4[4]	4[4]	5[4]	8[4]	11[4]
Intervention not Withdrawn[1]	0	0	0	0	0	2
Eligible[2]	211	210	204	200	195	189
Visit in Window	186	192	185	177	171	164
Visit Outside Window	17	11	11	18	19	24
No Visit	8	7	8	5	5	1

[1]Deaths, intervention, and withdrawn patients are cumulative over time.
[2]The number eligible is the number enrolled minus the number that died and the number that withdrew or were intervened.
[3]Three patients (08-212, 09-239, and 27-217) assigned to the Optimizer were too ill to receive the implant and died between 4 and 12 weeks from the study start date.
[4]Two patients assigned to the Control (13-204 and 13-215) and two patients assigned to the Optimizer (13-206 and 29-204) withdrew after randomization but prior to the study start date.

The reasons for study withdrawal by treatment group are presented in the table below.

Table V.2 Withdrawn Patients with Reason for Withdrawal by Study Group

Control Group		
Patient	**Study Days**[1]	**Reason for Discontinuation or Withdrawal**
13-215	-3	Subject and family members decided to see a cardiologist closer to their home.
13-204	0	Subject received heart transplant.
17-221	13	Patient did not wish to travel for control group
27-214	15	Subject called and requested withdrawal from the study.
36-215	35	Subject no longer wishes to take part in Optimizer Study
13-212	52	Patient not aware that he was on the Impulse Dynamics study
25-206	135	Patient has verbalized via telephone her refusal to continue participation.
27-209	150	Pt is noted to be non-compliant, refuses to return for follow up visits.
17-206	154	The patient underwent implant an ICD for cardiac resynchronization therapy.
13-228	301	Patient deemed completed prior to 50 week window.
20-231	318	Patient deemed completed prior to 50 week window.
06-204	324	Patient deemed completed prior to 50 week window.
17-217	327	Patient noncompliant with scheduled appointments.
43-208	329	Patient deemed completed prior to 50 week window.
13-218	331	Patient deemed completed prior to 50 week window.
18-202	331	Patient deemed completed prior to 50 week window.
20-222	332	Patient deemed completed prior to 50 week window.
21-218	332	Patient deemed completed prior to 50 week window.
23-205	334	Patient deemed completed prior to 50 week window.
37-219	334	Patient deemed completed prior to 50 week window.
14-202	335	Patient deemed completed prior to 50 week window.
48-205	335	Patient deemed completed prior to 50 week window.
Optimizer		
Patient	**Study Days**	**Reason for Discontinuation or Withdrawal**
29-204	-5	Patient himself chose to withdraw due to follow up compliance issues
13-206	-3	Patient withdrawn because patient wanted a second opinion.
22-202	8	Patient not implanted due to developed prolonged PR interval.
36-206	20	Patient was "too scared to proceed"
35-211	150	Patient's cardiologist chose to enroll in a different device trial.
37-211	194	Patient noncompliant with scheduled appointments.
12-205	210	Patient had implantation of an investigational LVAD
12-207	224	Patient underwent heart transplantation
12-208	306	Patient had heart transplant and removal of Optimizer device.
37-216	331	Patient deemed completed prior to 50 week window.
01-216	332	Patient deemed completed prior to 50 week window.

[1]Study days relative to study start date (SSD), which is the scheduled day of device implantation.

VI. Baseline Comparability

A comparison of baseline characteristics is given in the four tables below. The first comparison is for baseline quantitative variables such as age.

Table V I.1 Baseline Demographics – Quantitative Variables

Variable	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
Age (yrs)	58.55 (12.23) 213 59 (26, 86)	58.09 (12.79) 215 57 (19, 85)	0.5109[1]
QRS Duration (ms)[3]	101.51 (12.81) 212 102 (60, 130)	101.63 (15.30) 214 100 (70, 160)	0.5968[2]
PR Interval[4]	180.00 (31.59) 211 177.0 (24, 263)	181.04 (32.58) 214 179.0 (65, 272)	0.7155[1]
Holter (PVCs/24hr)	1365.1 (2000.9) 213 456.6 (0, 9960.5)	1323.3 (1930.6) 215 338.6 (0, 9298.0)	0.5113[1]
LVEF (%) (site)	26.09 (6.54) 213 27 (10, 35)	25.74 (6.60) 215 25 (10, 40)	0.5641[1]
LVEDD (mm) (site)[5]	63.01 (8.56) 211 62 (46, 88)	62.41 (9.22) 215 63 (30, 89)	0.7715[1]
MLWHFQ	57.38 (22.62) 213 59 (1, 102)	60.49 (23.00) 215 64 (0, 100)	0.1109[1]
6MW (meters)[6]	323.99 (92.44) 212 321 (80, 600)	326.38 (82.10) 215 330 (95, 525)	0.5971[1]
CPX (site)[7]			
Peak VO2 (ml/kg/min)	14.72 (2.86) 212 15.0 (9.0, 21.4)	14.81 (3.20) 215 14.7 (6.0, 25.9)	0.9784[1]
RER	1.13 (0.09) 212 1.11 (0.91, 1.43)	1.14 (0.10) 215 1.13 (0.96, 1.64)	0.3500[1]
Exercise Time (minutes)	11.59 (3.55) 212 11.67 (2.73, 22.00)	11.40 (3.25) 215 11.33 (4.00, 21.55)	0.4770[1]
Physical Exam			
Weight (kg)	93.30 (22.16) 213 90.9 (45.4, 169.0)	91.17 (23.27) 215 88.90 (44.7, 184.5)	0.1632[1]
Height (cm)	173.30 (9.71) 213 175.0 (142.0, 201.0)	172.77 (9.68) 215 173.0 (142.0 193.0)	0.5591[1]
BMI (kg/m2)	30.95 (6.53) 213 30.45 (18.63, 61.09)	30.44 (7.04) 215 29.65 (18.38, 60.99)	0.2179[1]
Resting HR (bpm)[8]	73.74 (12.19) 213 72.0 (49.0, 118.0)	73.98 (13.13) 214 72.0 (46.0, 115.0)	0.9681[1]
SBP (mmHg)[8]	115.61 (17.61) 213 114 (78, 174)	116.65 (19.48) 214 115 (78, 195)	0.8695[1]
DBP (mmHg)[8]	70.35 (10.66) 213 70.0 (44.0, 106.0)	71.32 (11.89) 214 70.0 (42.0, 119.0)	0.4690[1]
MBP[8]	85.43 (11.72) 213 84.67 (59.33, 119.33)	86.43 (13.31) 214 85.17 (54.67, 144.33)	0.6744[1]

[1]Two-sided Wilcoxon rank sum test.
[2]Two-sided unequal variance two-sample t-test.

[3]One patient from each group did not report a QRS duration.
[4]Two Control patients and one Optimizer patient did not report a PR interval.
[5]Two Control patients did not report LVEDD.
[6]One Control patient did not have a 6 minute walk time at baseline.
[7]One Control patient did not have any variable reported for the Site CPX.
[8]One Optimizer patient did not report heart rate or blood pressure at baseline.

The table above demonstrates that there are no statistically significant differences for baseline quantitative variables indicating good balance between the two study groups. The table below presents the comparison of baseline categorical variables such as gender.

Table VI.2 Baseline Demographics and Medical History Categorical Variables

Variable	Control n/N (%)	Optimizer n/N (%)	P-value
Male	151/213 (70.89)	158/215 (73.49)	0.5901[1]
Ethnicity			
White	142/213 (66.67)	154/215 (71.63)	0.5026[2]
Black	45/213 (21.13)	36/215 (16.74)	
Hispanic	19/213 (8.92)	13/215 (6.05)	
Asian	4/213 (1.88)	5/215 (2.33)	
Native American	1/213 (0.47)	2/215 (0.93)	
Other	2/213 (0.94)	5/215 (2.33)	
CHF Etiology			
Ischemic	142/213 (66.67)	139/215 (64.65)	0.6465[2]
Idiopathic	48/213 (22.54)	58/215 (26.98)	
Valvular	4/213 (1.88)	1/215 (0.47)	
Congenital	1/213 (0.47)	0/215 (0.00)	
Hypertrophic	3/213 (1.41)	4/215 (1.86)	
Peri/Postpardum	3/213 (1.41)	1/215 (0.47)	
Adriamycin	4/213 (1.88)	3/215 (1.40)	
Other	8/213 (3.76)	9/215 (4.19)	
Prior MI	126/213 (59.15)	125/215 (58.14)	0.8449[1]
Prior CABG	86/213 (40.38)	82/215 (38.14)	0.6923[1]
Prior PCI	83/213 (38.97)	86/215 (40.00)	0.8437[1]
Diabetes	102/213 (47.89)	91/215 (42.33)	0.2853[1]
NYHA (site)			
Class I	0 (0.0)	0 (0.0)	0.1720[2]
Class II	1/213 (0.47)	0/215 (0.00)	
Class III	183/213 (85.92)	196/215 (91.16)	
Class IV	29/213 (13.62)	19/215 (8.84)	

[1]Two-sided Fisher's exact test.
[2]Two-sided Pearson Chi-square test.

The table above demonstrates that there are no statistically significant differences for baseline categorical variables indicating good balance between the two study groups. The table below presents a comparison of baseline medication use.

Table VI.3 Baseline Medications

Medication	Control n/N (%)	Optimizer n/N (%)	P-Value[1]
Angiotensin converting enzyme inhibitor (ACEi)	148/213 (69.48)	153/215 (71.16)	0.7512
Angiotensin receptor blocker (ARB)	51/213 (23.94)	52/215 (24.19)	1.0000
ACEi or ARB	195/213 (91.55)	195/215 (90.70)	0.8654
Beta Blocker	198/213 (92.96)	202/215 (93.95)	0.7005
Loop Diuretic	194/213 (91.08)	198/215 (92.09)	0.7307
Second Diuretic[2]	12/210 (5.71)	19/212 (8.96)	0.2629
Aldosterone Inhibitor	102/213 (47.89)	95/215 (44.19)	0.4973
Hydralazine	15/213 (7.04)	12/215 (5.58)	0.5574
Nitrates	75/213 (35.21)	73/215 (33.95)	0.8391
Calcium Channel Blocker	9/213 (4.23)	18/215 (8.37)	0.1103
Anti-arrhythmic	28/213 (13.15)	37/215 (17.21)	0.2816

[1]Two-sided Fisher's exact test.
[2]Three control patients and three Optimizer patients did not have a second diuretic reponse.

The baseline medication usage is not statistically significantly different for any medication. The baseline core laboratory cardiopulmonary exercise assessments are compared in the table below.

Table VI.4 Baseline Cardiopulmonary Exercise (Core Laboratory)

Variable	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P –value
Duration (minutes)[3]	11.50 (3.46) 213 11.52 (2.73 20.13)	11.34 (3.20) 214 11.36 (3.30, 19.57)	0.4814[1]
Peak SBP (mmHg)[4]	138.8 (24.6) 212 140 (72, 210)	139.7 (27.1) 211 140 (80, 240)	0.9714[1]
Peak HR (bpm)[5]	121.2 (20.5) 212 121 (72, 176)	122.1 (20.2) 214 123 (72, 174)	0.5223[1]
Peak VO2 (ml/kg/min)[6]	14.71 (2.92) 211 15.00 (8.5, 22.6)	14.74 (3.06) 214 14.50 (8.4, 23.0)	0.8575[1]
Peak RER[7]	1.13 (0.09) 212 1.12 (0.91, 1.45)	1.14 (0.10) 214 1.12 (0.89, 1.57)	0.5189[1]
AT (ml/kg/min)[8]	10.97 (2.18) 207 10.7 (5.4, 17.0)	10.95 (2.24) 201 10.6 (5.3, 16.9)	0.9719[2]

[1]Two-sided Wilcoxon rank sum test.
[2]Two-sided unequal variance two-sample t-test.
[3]One Optimizer patient did not have a core lab report on exercise duration.
[4]One Control patient and four Optimizer patients did not have core lab report of baseline peak SBP.
[5]One Control patient and one Optimizer patient did not have core lab report of peak heart rate.
[6]Two Control patients and one Optimizer patient did not have a core lab report of peak VO2.
[7]One Control patient and one Optimizer patient did not have a core lab report of peak RER.
[8]Six Control patients and fourteen Optimizer patients did not have a core lab report of AT.

The baseline exercise capacity appears to be balanced between the treatment groups.

The data from all study sites will be pooled based on a clinical justification of pooling given in Meinert (1986). The pooling is based on three principles: that all sites used the same protocol, that the sponsor monitored the sites for protocol compliance and that the data gathering instruments (case report forms) were the same at all sites.

A comparison of the baseline characteristics by study site required by the Food and Drug Administration is provided below. Study sites were combined (to create pseudo sites) to allow a study site comparability assessment because a number of sites enrolled too few patients for analysis on their own. The method of forming pseudo-sites combines sites in numerical order in such a way to provide as much balance between treated and control patients within the pseudo site as possible. This process occasionally requires skipping the next site in order to have a better balance in the randomized patients between the two groups. The skipped site was combined with one or more sites below it that also provide a good balance for the randomized assignments to the control and Optimizer groups. The pseudo-sites and the original sites used to obtain the pseudo-site are presented below.

Table VI.5 Pseudo-site Formation from Original Study Sites

Pseudo Site Number	Originals Site Number(s)	Number of Control Patients	Number of Optimizer Patients	Total Patients
101	01 and 02	4	5	9
03	03	5	5	10
102	04 and 06	5	4	9
103	05 and 08	4	5	9
09	09	13	13	26
12	12	5	5	10
13	13	10	9	19
104	10, 14, and 18	5	5	10
15	15	6	6	12
17	17	8	9	17
105	19, 24, and 25	6	6	12
20	20	9	7	16
21	21	6	3	9
22	22	6	5	11
106	23 and 28	4	6	10
26	26	11	12	23
27	27	25	25	50
107	29 and 30	5	5	10
108	31, 34, 38, and 39	5	8	13
32	32	6	8	14
33	33	4	5	9
35	35	5	4	9
36	36	8	6	14
37	37	7	5	12
109	40, 44, and 48	7	7	14
41	41	17	17	34
110	42 and 43	4	5	9
111	45, 46, and 47	4	8	12
49	49	9	7	16
	Total	213	215	428

The analyses below use the general linear models procedure in SAS 9.1.3 to determine a site (pseudo-site) effect, treatment group effect, or an interaction for quantitative variables. For categorical variables, each variable was made binary by sub-grouping and the analysis of site, treatment and interaction was assessed by

logistic regression. In the tables below, the P-value for site, treatment, and interaction are presented. Any P-value less than 0.05 is to be included as a potential covariate for subsequent safety and effectiveness multivariate models.

Table VI.6 Summary of Study Site Comparability[1] for Baseline Quantitative Endpoints.

Variable	P-value for Treatment	P-value for Study Site[2]	P-value for Site by TRT Interaction
Age (yrs)	0.8898	**0.0358**	0.4392
QRS Duration (ms)	0.9860	**0.0140**	0.5862
PR Interval	0.5946	0.0671	0.3618
Holter (PVCs/24hr)	0.7084	0.1963	0.8410
LVEF (%) (site)	0.6279	**0.0080**	**0.0407**
LVEDD (mm) (site)	0.3354	**0.0089**	0.8733
MLWHFQ	0.3544	0.1093	0.6825
6MW (meters)	0.9201	**<0.0001**	0.4810
CPX (site)			
Peak VO2 (ml/kg/min)	0.8181	0.1801	0.6258
RER	0.8303	**0.0002**	0.9014
Exercise Time (minutes)	0.3910	**0.0006**	0.3362
Physical Exam			
Weight (kg)	0.2300	0.7073	0.8733
Height (cm)	0.4452	0.4173	0.0699
BMI (kg/m2)	0.3869	0.4334	0.9820
HR (bpm)	0.3611	0.3479	0.6336
SBP (mmHg)	0.5761	**0.0204**	0.8225
DBP (mmHg)	0.3488	0.1249	0.9863
MAP	0.4041	0.1620	0.9602

[1]Analysis by general linear models analysis of variance with Type III sums of squares.
[2]Pseudo-sites were used in this analysis and are defined in Table 4a.

Table VI.7 Summary of Study Site Comparability[1] for Baseline Categorical Endpoints.

Variable	P-value for Treatment	P-value for Study Site[2]	P-value for Site by TRT Interaction
Gender	0.5035	0.3753	0.7480
Ethnicity (White Versus Other)	0.4544	0.1526	0.8869
CHF Etiology	0.7791	0.9264	0.5019
Prior MI	0.4954	0.4563	0.3030
Prior CABG	0.4600	0.6964	0.2006
Prior PCI	0.5696	0.7694	0.5854
Diabetes	0.8448	0.3187	0.4951
NYHA (site)	0.7991	0.7948	0.3724

[1]Analysis by logistic regression.
[2]Pseudo-sites were used in this analysis and are defined in Table 4a.

Table VI.8 Summary of Study Site Comparability[1] for Baseline Medications.

Variable	P-value for Treatment	P-value for Study Site[2]	P-value for Site by TRT Interaction
ACEi	0.1089	0.5171	**0.0226**
ARB	0.4673	0.3345	0.4238
ACEi +/- ARB	0.0518	**0.0191**	**0.0261**
B-Blocker	0.5372	0.1887	0.6063
Diuretic	0.4026	0.9576	0.4637
Second Diuretic	**0.0122**	**0.0035**	**0.0161**
Aldosterone Inhibitor	0.1551	0.7007	0.2385
Antiarrhythmic	0.2260	0.3131	0.5036
Hydralazine	0.5334	0.9813	0.7634
Nitrates	0.8873	0.3973	0.6726
Ca Channel Blocker	0.2411	0.3480	0.9998

[1]Analysis by logistic regression.
[2]Pseudo-sites were used in this analysis and are defined in Table 4a.

Table VI.9 Summary of Study Site Comparability[1] for Baseline Cardiopulmonary Exercise

Variable	P-value for Treatment	P-value for Study Site[2]	P-value for Site by TRT Interaction
Duration (minutes)	0.4822	**0.0022**	0.2157
Peak SBP (mmHg)	0.7493	**<0.0001**	0.5936
Peak HR (bpm)	0.4134	**0.0223**	0.4897
Peak VO2 (ml/kg/min)	0.9894	0.6534	0.5938
Peak RER	0.7288	**0.0020**	0.9477
AT (ml/kg/min)	0.9690	0.3116	0.4726

[1]Analysis by general linear models analysis of variance with Type III sums of squares.
[2]Pseudo-sites were used in this analysis and are defined in Table 4a.

Because several baseline variables were significantly different between study sites, study pseudo-site will be used as a possible covariate in multivariate analyses below.

VII. Study Populations

The analysis populations are the intention to treat (ITT) consisting of all subjects randomized. The full analysis set A (FASA), consisting of all randomized patients but excluding patients who never received a study treatment (there were 7 Optimizer and 1 Control patient excluded in this population). The full analysis set B (FASB) consisting of all randomized patients excluding patients who did not receive a study treatment or had no study follow-up (there were 7 Optimizer and 6 Control patients excluded from this population). The population of completed cases (CC) consisting of all patients with a 24 week endpoint. The final population is the per protocol (PP) consisting of all CC patients who did not have a protocol violation that would

substantially affect study outcomes. Imputation by the methods described below is used to provide outcomes for effectiveness for subjects without outcomes in the ITT and FAS populations.

VIII. Comparison of Patient with Missing and Non-Missing Data

A comparison of the baseline characteristics between patients with missing data for the primary effectiveness variable and those without missing data are provided below. These test are intended to determine if there is evidence of not missing at random and if there is, to provide a remedy such that the missing data can be assumed to be missing at random for those patients for which imputation is planned. An initial analysis indicated that baseline weight, BMI, and site and core laboratory exercise durations were statistically significant. The weight variable was considered of lower importance, but the exercise duration could impact anaerobic threshold (AT, the primary effectiveness variable) and therefore indicated that, strictly speaking, the data are not missing at random. A review of the data indicated that the vast majority of exercise times exceeded 6-7 minutes and that subjects with short exercise times were less likely to show an improved AT regardless of treatment group. On that basis, any patient missing the 24 week PVO2 and/or 24 week AT was assigned a worst case score. This is similar to patients who had an event, i.e, patients who died or had an intervention (LVAD, heart transplant, or surgery to correct CHF) at a time that could be considered the reason why the data for 24 weeks was missing. There were 10 Active and 4 Control patients who had events prior to the 24 week visit and there were 3 Active and 6 Control patients who had an event between 24 and 50 weeks such that the event was considered the reason for missing the 24 week CPX. The inclusion of patients with missing 24 week data and a baseline core laboratory exercise time of less than 6.5 minutes results in 5 Active and 8 Control patients added to the worst score assignment list. The cumulative result is that 18 Active and 18 control patients had either the lowest AT value from any previous visit assigned, or if all AT values were missing for previous visits, the lowest AT value recorded for any randomized patient. These patients are indicated in Table IX.1 below as Imputation Case 6.

After removing the 13 cases with missing 24 week data and an exercise time less than 6.5 minutes, the baseline characteristic comparison between patients with missing and non-missing data at 24 weeks or baseline are presented in the following tables.

Table VIII.1 Baseline Demographics – Quantitative Variables - Compare Patients with Missing 24 Week AT data with those Not Missing 24 Week Data

Variable	Missing Mean (SD) N Med (Min, Max)	Non-Missing Mean (SD) N Med (Min, Max)	P-value
Age (yrs)	55.65 (14.42) 80 56.5 (19, 82)	58.93 (11.95) 348 59 (26, 86)	0.0673[2]
QRS Duration (ms)[3]	100.11 (14.03) 80 98.5 (72, 150)	101.91 (14.12) 346 102 (60, 150)	0.1325[1]
PR Interval[4]	175.45 (34.00) 80 174.0 (24, 248)	181.70 (31.53) 345 180.0 (65, 272)	0.2284[1]
Holter (PVCs/24hr)	1521.9 (2160.1) 80 438.6 (0, 8527.0)	1303.2 (1916.7) 348 411.6 (0, 9960.5)	0.4565[2]
LVEF (%) (site)	26.50 (6.42) 80 27 (11, 35)	25.78 (6.60) 348 25.5 (10, 40)	0.3368[1]
LVEDD (mm) (site)[5]	62.31 (8.58) 80 62 (42, 89)	62.80 (8.98) 346 63 (30, 88)	0.7555[1]
MLWHFQ	58.86 (22.73) 80 60 (2, 96)	58.96 (22.90) 348 63 (0, 102)	0.8365[1]
6MW (meters)[6]	321.96 (88.40) 79 334.0 (95, 585)	325.93 (87.15) 348 326 (80, 600)	0.7243[1]
CPX (site)[7]			
Peak VO2 (ml/kg/min)	14.60 (3.36) 79 14.2 (6.0, 25.9)	14.80 (2.96) 348 14.95 (9.0, 22.5)	0.4583[1]
RER	1.14 (0.09) 79 1.13 (0.91, 1.43)	1.13 (0.10) 348 1.12 (0.96, 1.64)	0.2218[1]
Exercise Time (minutes)	11.13 (3.49) 79 10.53 (4.0, 18.33)	11.58 (3.38) 348 11.75 (2.73, 22.00)	0.2186[1]
Physical Exam			
Weight (kg)	90.31 (23.99) 80 90.00(47.3, 140.9)	92.67 (22.44) 348 90.00 (44.7, 184.5)	0.3656[1]
Height (cm)	173.11 (10.84) 80 174.5 (142.0, 192.0)	173.02 (9.42) 348 173.0 (142.0 201.0)	0.5592[1]
BMI (kg/m2)	30.02 (7.37) 80 28.98 (18.38, 60.99)	30.85 (6.65) 348 30.18 (18.63, 61.09)	0.1955[1]
Resting HR (bpm)[8]	75.76 (12.11) 80 76.0 (50.0, 107.0)	73.42 (12.75) 347 72.0 (46.0, 118.0)	0.0655[1]
SBP (mmHg)[8]	117.15 (19.03) 80 118 (78, 178)	115.89 (18.46) 347 114 (78, 195)	0.4532[1]
DBP (mmHg)[8]	71.56 (12.63) 80 70.0 (48.0, 110.0)	70.67 (10.97) 347 70.0 (42.0, 119.0)	0.7129[1]
MBP[8]	86.76 (13.61) 80 87.00 (59.33, 132.67)	85.74 (12.29) 347 84.67 (54.67, 144.33)	0.5171[1]

[1]Two-sided Wilcoxon rank sum test.
[2]Two-sided unequal variance two-sample t-test.
[3]Two patients with non-missing data did not report QRS duration.
[4]Three patients with non-missing data did not report a PR interval.
[5]Two patients with non-missing data did not report LVEDD.
[6]One patient with missing data did not have a 6 minute walk time at baseline.
[7]One patient with missing data did not have any variable reported for the Site CPX.
[8]One patient with non-missing data did not report heart rate or blood pressure at baseline.

Thus, there are no statistically significant differences in the quantitative baseline characteristics between the missing and non-missing patients.

Table VIII.2 Baseline Demographics and Medical History Categorical Variables - Compare Patients with Missing 24 Week AT data with those Not Missing 24 Week Data

Variable	Missing n/N (%)	Non Missing n/N (%)	P-value[1]
Male	58/80 (72.50)	251/348 (72.13)	1.0000
Ethnicity (White)	52/80 (65.00)	244/348 (70.11)	0.4207
CHF Etiology (Ischemic)	32/80 (40.00)	115/348 (33.05)	0.2426
Prior MI	44/80 (55.00)	207/348 (59.48)	0.5292
Prior CABG	30/80 (37.50)	138/348 (39.66)	0.7998
Prior PCI	30/80 (37.50)	139/348 (39.94)	0.7058
Diabetes	38/80 (47.50)	155/348 (44.54)	0.7088
NYHA (site) (Class IV)	11/80 (13.75)	37/348 (10.63)	0.4334

[1]Two-sided Fisher's exact test.

Table VIII.3 Baseline Medications - Compare Patients with Missing 24 Week AT data with those Not Missing 24 Week Data

Medication	Missing n/N (%)	Non-Missing n/N (%)	P-Value[1]
Angiotensin converting enzyme inhibitor (ACEi)	58/80 (72.50)	243/348 (69.83)	0.6856
Angiotensin receptor blocker (ARB)	18/80 (22.50)	85/348 (24.43)	0.7733
ACEi or ARB	72/80 (90.00)	318/348 (91.38)	0.6660
Beta Blocker	72/80 (90.00)	328/348 (94.25)	0.2060
Loop Diuretic	76/80 (95.00)	316/348 (90.80)	0.2701
Second Diuretic	9/80 (11.25)	22/348 (6.32)	0.1489
Aldosterone Inhibitor	35/80 (43.75)	162/348 (46.55)	0.7096
Hydralazine	7/80 (8.75)	20/348 (5.75)	0.3122
Nitrates	27/80 (33.75)	121/348 (34.77)	0.8970
Calcium Channel Blocker	4/80 (5.00)	23/348 (6.61)	0.7994
Anti-arrhythmic	4/80 (5.00)	61/348 (17.53)	**0.0031**

[1]Two-sided Fisher's exact test.

Only anti-arrhythmic medication use was statistically significantly difference between the missing and non-missing groups. The non-missing group had the higher rate of anti-arrhythmic medication use.

Table VIII.4 Baseline Cardiopulmonary Exercise (Core Laboratory) - Compare Patients with Missing 24 Week AT data with those Not Missing 24 Week Data

Variable	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P –value
Duration (minutes)[3]	11.22 (3.50) 80 10.48 (4.92, 18.82)	11.47 (3.29) 347 11.65 (2.73, 20.13)	0.3570[1]
Peak SBP (mmHg)[4]	139.9 (24.3) 80 140 (96, 210)	139.1 (26.2) 343 140 (72, 240)	0.7116[1]
Peak HR (bpm)[5]	124.0 (20.4) 80 123.5 (72, 173)	121.1 (20.3) 346 121 (72, 176)	0.2372[1]
Peak VO2 (ml/kg/min)[6]	14.69 (2.99) 78 14.65 (8.4, 21.7)	14.73 (3.00) 347 14.80 (8.5, 23.0)	0.8189[1]
Peak RER[7]	1.13 (0.11) 79 1.12 (0.89, 1.52)	1.13 (0.09) 347 1.12 (0.97, 1.57)	0.7702[2]
AT (ml/kg/min)[8]	11.00 (1.99) 64 10.6 (7.4, 15.6)	10.95 (2.25) 344 10.7 (5.3, 17.0)	0.7541[1]

[1]Two-sided Wilcoxon rank sum test.
[2]Two-sided unequal variance two-sample t-test.
[3]One non-missing patient did not have a core lab report on exercise duration.
[4]Five non-missing patients did not have core lab report of baseline peak SBP.
[5]Two non-missing patients did not have core lab report of peak heart rate.
[6]Two missing patients and one non-missing patient did not have a core lab report of peak VO2.
[7]One missing patient and one non-missing patient did not have a core lab report of peak RER.
[8]Sixteen missing patients and four non-missing patients did not have a core lab report of AT.

Exercise testing was not statistically significantly different between the missing and non-missing patients after deleting missing patients with less than 6.5 minute of baseline exercise duration. These tests do not provide evidence that the missing at random assumption for the imputations below is violated.

IX. Imputation Methods

There are several methods of imputation that could be applied to missing data based on what data are missing and the relationships of the missing observations to data that are present. The proposed method of imputation depends on the amount of data that are present for any given subject as summarized in the following table, and detailed below.

Table IX.1 Imputation Cases from Statistical Analysis Plan

CASE	Baseline		6 Month Follow-Up		Imputation Method	Patients in Case	
	Peak VO2	AT	Peak VO2	AT		Treatment	Control
0	Present	Present	Present	Present	None	159	153
1	Present	Present	Present	Absent	Stochastic regression based on PVO2 and RER at 6M	8	9
2	Present	Absent	Present	Present	Stochastic regression based on PVO2 and RER at Baseline	10	2
3	Present	Absent	Present	Absent	Stochastic regression based on ΔPVO2 and RER	1	0
4	Present	Present	Absent	Absent	Propensity Matching and Random Selection	18	29
5	Present	Absent	Absent	Absent	Propensity Matching and Random Selection	1	2
6	Patients died, had an event, or had missing data and baseline duration <6.5 minutes[1]					18	18

[1]A comparison of exercise duration between patients with missing and non-missing 24 week AT data indicated that subjects missing 24 week data with short baseline exercise times (<6.5 minutes) were possibly not missing at random. Assigning these patients worst case values and removing them from the missing patient comparison resulted in no statistically significant differences between the patients with missing and non-missing 24 week AT values demonstrating that there is no violation in the missing at random assumption.

a. Regression Imputations

For the patients in groups 1-3 above, the regression analysis of the completed cases resulted in the coefficients presented in the table below.

Table IX.2 Regression Results for Imputation

Imputation Case 1	**Intercept**	**Coefficient of PVO2 (6 Mo.)**	**Coefficient of RER (6 Mo.)**	**Root Residual Mean Square**
6-Mo AT Missing Control	9.138	0.538	-5.502	1.170
6-Mo AT Missing Optimizer	4.163	0.597	-1.945	1.132
Imputation Case 2	**Intercept**	**Coefficient of PVO2 (BL)**	**Coefficient of RER (BL)**	**Root Residual Mean Square**
Baseline AT Missing Control	6.421	0.619	-3.888	1.176
Baseline AT Missing Optimizer	6.534	0.613	-4.096	1.127
Imputation Case 3	**Intercept**	**Coefficient of ΔPVO2 (6 Mo.)**	**Coefficient of ΔRER (6 Mo.)**	**Root Residual Mean Square**
Baseline and 6-Month AT Missing Control	-0.075	0.571	-4.212	1.300
Baseline and 6-Month AT Missing Optimizer	-0.118	0.614	-1.499	1.270

The imputed value is obtained by generating a standard normal value, z, and then applying the formula below for cases 1 and 2.

$$AT = z*s + a + b_1* PVO2 + b_2 *RER$$

Where s is the root mean square from the regression (an estimate of the standard deviation of the AT value), a is the intercept, $b_1$is the coefficient for PVO2 and b_2 is the coefficient for RER. The equation for case three is similar with the difference that the AT term being estimated and the PVO2 and RER values are differences between 24 weeks and baseline.

b. Propensity Score Imputation (Imputation Cases 4 and 5)

The patients who had both PVO2 and AT at 24 week missing were assigned to Imputation Case 4. In addition to the one patient missing AT at baseline, and PVO2 and AT at 24 weeks, one patient missing PVO2 and AT at baseline and PVO2 at 24 weeks and a second patient missing PVO2 and AT at baseline were added to Imputation Case 5. Because there were only three patients in Case 5, these were added to Case 4 for propensity score assignment and subsequent imputation. The random selection based on the propensity score quintile replaced only the missing values for any patient. For the purposes of

modeling missingness, patients in the combined Cases 4 and 5 were assigned a missingness indicator and all other patients were assigned an indicator that data were not missing. The propensity scores were assigned modeling the missingness of the combined Cases 4 and 5 by non-parsimonious logistic regression. The model estimates are provided in the table below.

Table IX.3 Non-parsimonious Model for Propensity Score Imputation

Baseline Covariate*	Estimated Coefficient	P-value
Age	-0.0237	0.1129
Treatment Group	0.2644	0.0914
Gender (Female)	0.00976	0.9569
CHF Etiology (Ischemic)	0.0584	0.7557
Diabetic	-0.1579	0.3209
LVEF (Site)	0.0215	0.3739
Baseline MLWHFQ	-0.0134	0.0635
NYHA (Class IV)	0.0503	0.8356
Baseline PVO2	0.0204	0.7150
Baseline RER	0.5316	0.7460

*Only covariates that have date for at least 90% of patients will be used and missing data will be imputed by substituting the median by treatment group for the missing variable. Propensity score covariates can have no missing values.

The random selection was done from quintiles of patients with actual non-missing data based on propensity scores and the numbers of missing, assumed non-missing (patients not in Case 4 or 5) and actual non-missing patients (the subset of patients not in Cases 4 or 5 with non-missing data) are presented in the table below.

Table IX.4 Distribution of Patients by Treatment and Propensity Score Quintile

Quintile	Missing n/N (%)	Not Case 4 or 5	Not Missing
1	2/50 (4.00)	84/378 (22.22)	75/348 (21.55)
2	12/50 (24.00)	74/378 (19.58)	67/348 (19.26)
3	11/50 (22.00)	74/378 (19.58)	70/348 (20.11)
4	8/50 (16.00)	78/378 (20.63)	72/348 (20.69)
5	17/50 (34.00)	68/378 (17.99)	64/348 (18.39)

This table demonstrates that there is a more than ample set of patients with complete data from which the patients with missing data can obtain values in each quintile. The random selection is done with replacement.

X. Primary Safety Analysis

The primary safety analysis evaluated the composite event rate of all cause mortality and all cause hospitalization at 50 weeks. The statistical hypothesis is that the proportion of subjects in the treatment group where an event occurs by the 50 weeks will be non-inferior to the proportion of subjects where an event occurs by the 50 weeks in the control group. The statistical hypothesis to be tested is:

H_0: $\pi_t > \pi_c + \delta$

vs.

H_1: $\pi_t \leq \pi_c + \delta$

where δ=0.125 (clinically insignificant difference) and π_c is the event rate in the control group and the π_t is the event rate in the treatment group. The statistical test to be used shall be the Blackwelder (1982) non-inferiority test and will be evaluated based on the intent-to-treat subject population.

The events comprising the composite primary safety endpoints are provided in the table below for all patients, for patients grouped by core lab ejection fraction (< 25 or ≥ 25), and patients grouped by core lab ejection fraction and NYHA (equal to 3 or not).

Table X.1 Primary Safety Events (Deaths or All Cause Hospitalizations) for the ITT Population

Group	Control n/N (%)	Optimizer n/N (%)	P-Value[1]
All	103/213 (48.36)	112/215 (52.09)	**0.0348**
BL EF[2]<25	50/99 (50.50)	56/98 (57.14)	0.2041
BL EF[2]≥25	53/113 (46.90)	56/117 (47.86)	**0.0399**
BL EF[2]<25 & NYHA ≠3	9/14 (64.29)	7/11 (63.64)	0.2484
BL EF[2]<25 & NYHA=3	41/85 (48.24)	49/87 (56.32)	0.2805
BL EF[2]≥25 & NYHA ≠3	11/16 (68.75)	4/8 (50.00)	.0.0696
BL EF[2]≥25 & NYHA=3	42/97 (43.30)	52/109 (47.70)	0.1219

[1]One-sided Blackwelder's test for non-inferiority with δ = 0.125
[2]One Control patient did not have a baseline core laboratory ejection fraction

There were 103 events in the control group and 112 events in the Optimizer group by 50 weeks. If one applies the Blackwelder test to the ITT population, assuming those lost to follow-up did not have an event, the rate in the control arm is 103/213 = 0.4836 and in the test arm is 112/215=0.5209. The difference is 0.0374 and the Blackwelder z-statistic is -1.8143 which corresponds to a P-value of 0.0348. The upper one-sided 95% confidence limit is 11.68 which is below the delta of 12.5. Under this test, the primary safety endpoint is met.

Recognizing that 6 control patients and 7 Optimizer patients either died or withdrew early with no follow-up beyond the screening examination, the modified ITT

population has 207 control and 208 Optimizer patients. The events in this population are presented in the table below.

Table X.2 Primary Safety Events (Deaths or All Cause Hospitalizations) for the m-ITT Population

Group	Control n/N (%)	Optimizer n/N (%)	P-Value[1]
All	103/207 (49.76)	112/208 (53.85)	**0.0431**
BL EF[2]<25	50/98 (51.02)	56/96 (58.33)	0.2334
BL EF[2]≥25	53/108 (49.07)	56/112 (50.00)	**0.0430**
BL EF[2]<25 & NYHA ≠3	9/14 (64.29)	7/11 (63.64)	0.2484
BL EF[2]<25 & NYHA=3	41/84 (48.81)	49/85 (57.65)	0.3160
BL EF[2]≥25 & NYHA ≠3	11/15 (73.33)	4/8 (50.00)	0.0443
BL EF[2]≥25 & NYHA=3	42/93 (45.16)	52/104 (50.00)	0.1409

[1]One-sided Blackwelder's test for non-inferiority with δ = 0.125
[2]One Control patient did not have a baseline core laboratory ejection fraction

An analysis of the primary safety endpoint in this population results in 103/207 = 0.4976 in the control group and 112/208 = 0.5385 in the Optimizer group. The difference is 0.0409 and the Blackwelder z-statistic is -1.7163 which corresponds to a P-value of 0.0431. The upper one-sided 95% confidence limit is 12.15 which is below the delta of 12.5. Under this test in the m-ITT population, the primary safety endpoint is met.

There was 1 additional control patient that was a clear protocol violation and 4 Optimizer patients who refused treatment but continued with study follow-up visits. Excluding these additional subjects from the m-ITT population yields the per protocol population (PP) for safety of 206 control and 204 Optimizer patients. The events for this population are presented in the table below.

Table X.3 Primary Safety Events (Deaths or All Cause Hospitalizations) for the PP Population

Group	Control n/N (%)	Optimizer n/N (%)	P-Value[1]
All	102/206 (49.51)	109/204 (53.43)	**0.0409**
BL EF[2]<25	49/97 (50.52)	55/95 (57.89)	0.2376
BL EF[2]≥25	53/108 (49.07)	54/109 (49.54)	**0.0381**
BL EF[2]<25 & NYHA ≠3	9/14 (64.29)	7/11 (63.64)	0.2484
BL EF[2]<25 & NYHA=3	40/83 (48.19)	48/84 (57.14)	0.3223
BL EF[2]≥25 & NYHA ≠3	11/15 (73.33)	4/8 (50.00)	0.0443
BL EF[2]≥25 & NYHA=3	42/93 (45.16)	50/101 (49.50)	0.1276

[1]One-sided Blackwelder's test for non-inferiority with δ = 0.125
[2]One Control patient did not have a baseline core laboratory ejection fraction

The one control and 3 of the 4 Optimizer patients experienced events so the number of events for the PP population is 102 in the control group and 109 in the Optimizer group. An analysis of the primary endpoint with the PP population yields 102/206 = 0.4951 in the control group and 109/204 = 0.5343 in the Optimizer group. The difference is 0.0392 and the Blackwelder z-statistic for this test is -1.7400 which corresponds to a P-value of 0.0409. The upper one-sided 95% confidence limit is

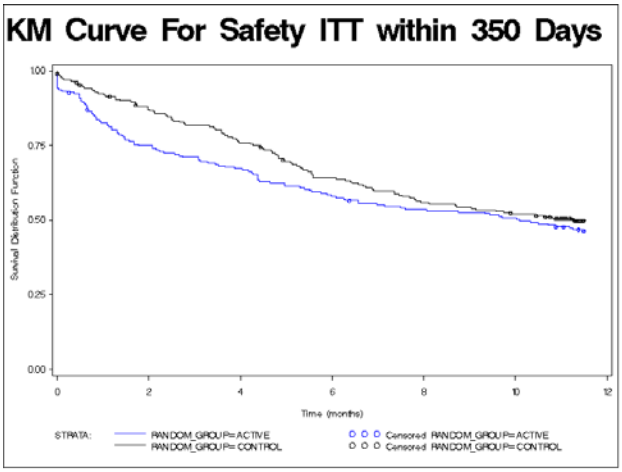
12.03 which is below the delta of 12.5. Under this test in the PP population, the primary safety endpoint is met.

Thus the primary safety null hypothesis is rejected under any of the three test conditions, ITT, m-ITT, or PP.

XI. Secondary Safety Analyses

Kaplan-Meier (KM) analyses were done for the composite for all patients in the ITT, m-ITT, and PP populations. The KM analysis for all ITT subjects appear in the figure below. The freedom from event curves with not statistically different from each other with a log-rank P-value = 0.2229.

Figure 1. Kaplan Meier Analysis of the Composite Primary Safety Endpoint of Death of Hospitalization in 350 days for the ITT Population,.



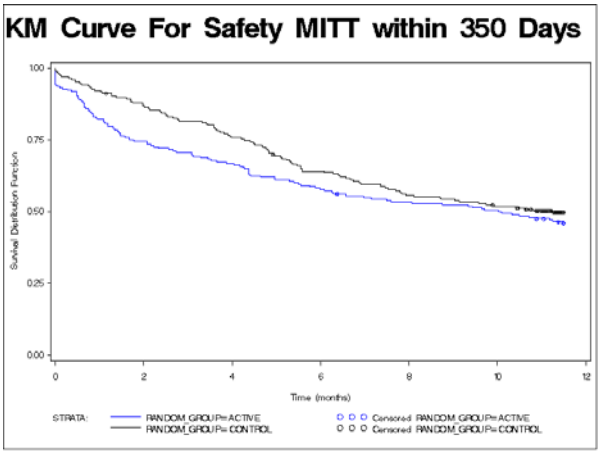
The table below presents the freedom from even rates and 95% confidence intervals.

Table XI.1 Estimated Rates of Freedoms from Primary Safety Event through 350 Days (ITT)

Treatment Group	Month	Patients Remaining	Proportion Free from AE	Lower 95% CL	Upper 95% CL
Control	0	212	1	--	--
	1	193	0.9239	0.8880	0.9598
	3	169	0.8177	0.7652	0.8702
	6	131	0.6424	0.5769	0.7079
	12	67	0.4988	0.4302	0.5674
Optimizer	0	209	1	--	--
	1	181	0.8270	0.7756	0.8784
	3	147	0.7109	0.6492	0.7726
	6	120	0.5803	0.5131	0.6475
	12	92	0.4630	0.3950	0.5310

The KM analysis of the m-ITT population is presented in the figure and table below. The two curves were not significantly different from each other with a log-rank P-value of 0.2134.

Figure 2. Kaplan Meier Analysis of the Composite Primary Safety Endpoint of Death of Hospitalization in 350 days for the m-ITT Population.



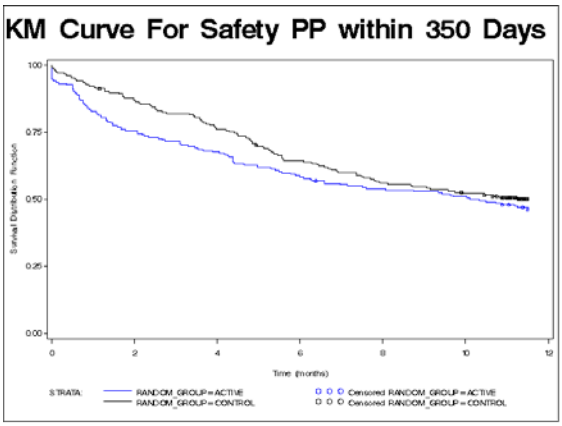
The table below presents the freedom from even rates and 95% confidence intervals.

Table XI.2 Estimated Rates of Freedoms from Primary Safety Event through 350 Days (m-ITT)

Treatment Group	Month	Patients Remaining	Proportion Free from AE	Lower 95% CL	Upper 95% CL
Control	0	207	1	--	--
	1	191	0.9227	0.8862	0.9592
	3	168	0.8169	0.7640	0.8698
	6	131	0.6407	0.5752	0.7062
	12	67	0.4974	0.4288	0.5660
Optimizer	0	208	1	--	--
	1	171	0.8221	0.7702	0.8740
	3	147	0.7067	0.6448	0.7686
	6	120	0.5769	0.5097	0.6441
	12	92	0.4603	0.3925	0.5281

The KM curve for the PP population is presented in the figure and table below. Two freedom from event curves are not statistically significantly different from each other with a log-rank P-value of 0.2460.

Figure 3. Kaplan Meier Analysis of the Composite Primary Safety Endpoint of Death of Hospitalization in 350 days for the PP Population.



The table below presents the freedom from even rates and 95% confidence intervals.

Table XI.3 Estimated Rates of Freedoms from Primary Safety Event through 350 Days (PP)

Treatment Group	Month	Patients Remaining	Proportion Free from AE	Lower 95% CL	Upper 95% CL
Control	0	206	1	--	--
	1	190	0.9223	0.8858	0.9588
	3	168	0.8199	0.7674	0.8724
	6	131	0.6438	0.5781	0.7095
	12	67	0.4999	0.4311	0.5687
Optimizer	0	208	1	--	--
	1	169	0.8284	0.7767	0.8801
	3	146	0.7157	0.6538	0.7776
	6	119	0.5833	0.5157	0.6509
	12	91	0.4644	0.3958	0.5330

A Cox regression multivariate analysis was done on the primary safety endpoint (all cause mortality and hospitalization) for events through 350 days.

Variables were screened by the method of Hosmer and Lemeshow (2000) with a P-value for admission into competition for the final model of 0.2. Univariate Cox models including the covariate of interest and its interaction with treatment were used for screening. If the interaction term with treatment is not significant, a second model was done without the interaction to screen for the main effect.

The variables that were screened and their corresponding P-values are presented in the table below.

Table XI.4 Univariate Cox Regression Model Screening of Covariates for Primary Safety Events through 350 Days from Study Start Date (m-ITT)

Characteristic	P-value[1]
Age	**0.0785**
Age by Optimizer Treatment Interaction	0.8009

Gender	0.3246
Gender by Optimizer Treatment Interaction	0.4149
Baseline PVO2	0.9940
Baseline PVO2 by Optimizer Treatment Interaction	0.4311
Baseline AT	0.8637
Baseline AT by Optimizer Treatment Interaction	0.7270
Baseline Peak RER	0.5796
Baseline Peak RER by Optimizer Treatment Interaction	0.8730
Baseline Ejection Fraction (Quantitative)	0.6542
Baseline Ejection Fraction by Optimizer Treatment Interaction	0.9854
Baseline Ejection Fraction (Categorical Cut at 25)	0.4676
Baseline Ejection Fraction by Optimizer Treatment Interaction	0.6737
Diabetes	**0.0982**
Diabetes by Optimizer Treatment Interaction	0.2642
Baseline NYHA (Site)	**0.0779**
Baseline NYHA by Optimizer Treatment Interaction	0.2845
Baseline NYHA (Site) (NYHA = 3 or Not)	**0.0779**
Baseline NYHA by Optimizer Treatment Interaction	0.2845
CHF Etiology	--[2]
CHF Etiology by Optimizer Treatment Interaction	--[2]
Baseline MLWHFQ	**0.0445**
Baseline MLWHFQ by Optimizer Treatment Interaction	0.2504
BMI	0.7600
BMI by Optimizer Treatment Interaction	0.8891
Race (White)	0.7382
Race by Optimizer Treatment Interaction	**0.0506**
PTCA or CABG	0.3363
PTCA or CABG by Optimizer Treatment Interaction	0.2056
Baseline Core Lab Exercise Duration	**0.0912**
Baseline Core Lab Exercise Duration by Optimizer Treatment Interaction	0.3932
Pseudo-Site	0.5091
Pseudo-Site by Optimizer Treatment Interaction	0.7444

[1]Covariates with P-values ≤0.20 are allowed to enter the competition for the final model (bold face in table). If the interaction is not significant, the P-value reported is for the model with the main effect only.
[2]The model for CHF etiology did not have a solution so no P-value is reported.

The final model appears was determined by manual backward elimination and the result is presented in the table below. Eight variables were included in the competition for the final model including age, diabetes, baseline NYHA (continuous or categorical), baseline MLWHFQ, race, and race by treatment interaction.

Table 2.2.6 Multivariate Cox Regression Final Model Results for Mortality

Factor	Hazard Ratio	95% CL on HR	P-Value*
Race (White)	0.712	0.535-0.947	**0.0197**

The treatment term was the last term removed from the model and its P-value at removal was 0.1627. This analysis implies that the only covariate associated with the primary safety composite endpoint of all cause death or hospitalization is race with Caucasians having a lower risk of death or hospitalization than non-Caucasians. Stepwise regression was applied to provide a verification of this models and the same model resulted from that application.

XII. Primary Effectiveness Analysis

For the primary effectiveness analysis, imputation was necessary to obtain study outcomes for patients that did not have an endpoint at 24 weeks. The imputation was done by the methods described in Section IX above. Ten imputations for the ITT patients appear in the tables below. First the means are presented and then the responder analysis (with a responder defined a subject whose AT increased by ≥20%).

Table XII.1a Mean AT at Study Time Points

Imputation	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
ITT1	Baseline	10.90 (2.29) 213 10.56 (4.10, 17.05)	10.89 (2.32) 215 10.60 (4.10, 16.92)	0.9840[1]
	24 Week[3]	10.74 (2.27) 213 10.78 (4.10, 19.61)	10.81 (2.44) 214 10.40 (4.10, 19.82)	0.7505[1]
	24 Week Difference From Baseline	-0.15 (2.25) 213 -0.17 (-7.29, 9.34)	-0.08 (2.35) 215 -0.09 (-6.91, 9.17)	0.3670[2]
ITT2	Baseline	10.90 (2.26) 213 10.65 (4.10, 17.05)	10.87 (2.34) 215 10.59 (4.10, 16.92)	0.8966[1]
	24 Week[3]	10.74 (2.25) 213 10.72 (4.10, 19.61)	10.80 (2.49) 214 10.42 (4.10, 19.82)	0.7855[1]
	24 Week Difference From Baseline	-0.16 (2.25) 213 -0.17 (-5.68, 9.34)	-0.08 (2.29) 215 -0.11 (-6.55, 8.94)	0.3484[2]
ITT3	Baseline	10.92 (2.28) 213 10.72 (4.10, 17.05)	10.88 (2.30) 215 10.60 (4.10, 16.92)	0.8576[1]
	24 Week[3]	10.79 (2.28) 213 10.61 (4.10, 19.61)	10.78 (2.46) 214 10.40 (4.10, 19.82)	0.9688[1]
	24 Week Difference From Baseline	-0.12 (2.27) 213 -0.17 (-6.10, 9.34)	-0.09 (2.29) 215 -0.09 (-6.47, 8.94)	0.4444[2]
ITT4	Baseline	10.90 (2.27) 213 10.73 (4.10, 17.05)	10.88 (2.29) 215 10.59 (4.10, 16.92)	0.9382[1]
	24 Week[3]	10.72 (2.30) 213 10.53 (4.10, 19.61)	10.81 (2.51) 214 10.42 (4.10, 19.82)	0.3122[1]
	24 Week Difference From Baseline	-0.19 (2.27) 213 -0.12 (-6.03, 9.34)	-0.08 (2.35) 215 -0.09 (-6.47, 8.94)	0.6878[2]
ITT5	Baseline	10.93 (2.28) 213 10.73 (4.10, 17.05)	10.89 (2.30) 215 10.59 (4.10, 16.92)	0.8492[1]
	24 Week[3]	10.69 (2.31) 213 10.53 (4.10, 19.61)	10.81 (2.42) 214 10.49 (4.10, 19.82)	0.6081[1]
	24 Week Difference From Baseline	-0.24 (2.19) 213 -0.13 (-8.59, 9.34)	-0.08 (2.28) 215 -0.09 (-6.88, 8.94)	0.2390[2]
ITT6	Baseline	10.89 (2.27) 213 10.65 (4.10, 17.05)	10.87 (2.29) 215 10.59 (4.10, 16.92)	0.9170[1]
	24 Week[3]	10.69 (2.28) 213 10.64 (4.10, 19.61)	10.74 (2.56) 214 10.39 (4.10, 19.82)	0.8389[1]
	24 Week Difference From Baseline	-0.21 (2.23) 213 -0.17 (-5.13, 9.34)	-0.14 (2.41) 215 -0.14 (-8.23, 8.94)	0.3898[2]
ITT7	Baseline	10.88 (2.30) 213 10.65 (4.10, 17.05)	10.90 (2.33) 215 10.60 (4.10, 16.92)	0.9253[1]
	24 Week[3]	10.81 (2.29) 213 10.80 (4.10, 19.61)	10.78 (2.46) 214 10.42 (4.10, 19.82)	0.9088[1]
	24 Week Difference From Baseline	-0.07 (2.32) 213 -0.10 (-6.65, 9.34)	-0.12 (2.33) 215 -0.07 (-7.99, 8.94)	0.5948[2]
ITT8	Baseline	10.95 (2.28) 213 10.73 (4.10, 17.05)	10.83 (2.33) 215 10.59 (4.10, 16.92)	0.5965[1]
	24 Week[3]	10.68 (2.27) 213 10.53 (4.10, 19.61)	10.70 (2.49) 214 10.38 (4.10, 19.82)	0.9248[1]
	24 Week Difference From Baseline	-0.27 (2.23) 213 -0.22 (-6.71, 9.34)	-0.13 (2.40) 215 -0.16 (-6.91, 8.94)	0.2711[2]

Table XII.1a Mean AT at Study Time Points (Continued)

Imputation	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
ITT9	Baseline	10.94 (2.28) 213 10.73 (4.10, 17.05)	10.89 (2.30) 215 10.59 (4.10, 16.92)	0.8402[1]
	24 Week[3]	10.72 (2.21) 213 10.72 (4.10, 19.61)	10.80 (2.50) 214 10.40 (4.10, 19.82)	0.7000[1]
	24 Week Difference From Baseline	-0.22 (2.14) 213 -0.23 (-5.04, 9.34)	-0.08 (2.26) 215 -0.14 (-6.51, 8.94)	0.2645[2]
ITT10	Baseline	10.89 (2.28) 213 10.56 (4.10, 17.05)	10.88 (2.29) 215 10.57 (4.10, 16.92)	0.9462[1]
	24 Week[3]	10.69 (2.33) 213 10.64 (4.10, 19.61)	10.79 (2.45) 214 10.46 (4.10, 19.82)	0.6547[1]
	24 Week Difference From Baseline	-0.21 (2.34) 213 -0.13 (-8.59, 9.34)	-0.08 (2.25) 215 -0.17 (-6.47, 8.94)	0.2845[2]

[1]Two-sided equal variance Student's t-test.
[2]One-sided equal variance Student's t-test
[3]One patient in the Optimizer group had a difference imputed but did not have a 24 week AT imputed.

The responder analysis for the 10 imputations appears below.

Table XII.1b Univariate Primary Effectiveness Endpoint Results (≥20% Improvement) for ITT Patients

Population	Control n/N (%)	Optimizer n/N (%)	P-value[1]
ITT1	28/213 (13.15)	37/215 (17.21)	0.1500
ITT2	31/213 (14.55)	37/215 (17.21)	0.2681
ITT3	29/213 (13.62)	38/215 (17.67)	0.1533
ITT4	26/213 (12.21)	39/215 (18.14)	0.0573
ITT5	27/213 (12.68)	40/215 (18.60)	0.0598
ITT6	26/213 (12.21)	36/215 (16.74)	0.1157
ITT7	30/213 (14.08)	36/215 (16.74)	0.2652
ITT8	24/213 (11.27)	39/215 (18.14)	0.0304
ITT9	27/213 (12.68)	40/215 (18.60)	0.0598
ITT10	33/213 (15.49)	38/215 (17.67)	0.3169

[1]One-sided Fisher's exact test

Rubin (1987) indicates that the data from multiple imputations can be combined to get an overall test of significance. The method is the basis of Proc MIANALYZE in SAS and is described in the online manual SAS OnlineDoc Version 8, Chapter 10 (Proc MIANALYZE), page 211.

The procedure computes the mean difference across all imputations by the following formula

$$\overline{Q} = \frac{1}{m}\sum_{i=1}^{m}\hat{Q}_i$$

where Q_i is the difference between the Optmizer proportion and the control proportion for the ith imputation and m is the number of imputations (M=10 here)

The variance is computed as a function of the within imputation variance and the between imputation variance. The estimate of the within imputation variance is given by the following.

$$\overline{U} = \frac{1}{m}\sum_{i=1}^{m}\hat{U}_i$$

where U_i is the variance of the difference in the ith imputation and is given by the following.

$$U_i = \frac{p_{it}(1-p_{it})}{229} + \frac{p_{ic}(1-p_{ic})}{231}$$

and p_{it} and p_{ic} are the proportions of patient with serious or significant adverse events in the Optimizer and Control groups respectively.

The between imputation variance is obtained by the following formula.

$$B = \frac{1}{m-1}\sum_{i=1}^{m}\left(\hat{Q}_i - \overline{Q}\right)^2$$

The total variance in given by the following formula.

$$T = \overline{U} + (1+\frac{1}{m})B$$

and the z-statistic is given by the following.

$$z = \frac{(\overline{Q})}{\sqrt{T}}$$

When these imputations are combined the z = -0.4839 with a corresponding P-value of 0.3142.

The mean values for the ITT ten imputations for patients with baseline EF≥25 are presented below.

Table XII.2a Mean AT at Study Time Points with EF ≥25 at Baseline

Imputation	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
ITT1	Baseline	11.14 (2.31) 113 10.73 (5.40, 17.05)	10.76 (2.12) 117 10.44 (5.29, 16.08)	0.1909[1]
	24 Week	10.69 (2.09) 113 10.64 (4.79, 15.50)	10.95 (2.38) 117 10.50 (5.01, 19.82)	0.3763[1]
	24 Week Difference From Baseline	-0.45 (2.02) 113 -0.33 (-7.29, 5.64)	0.19 (2.45) 117 -0.08 (-4.65, 9.17)	**0.0152**[2]
ITT2	Baseline	11.17 (2.29) 113 10.76 (5.40, 17.05)	10.74 (2.18) 117 10.44 (5.29, 16.09)	0.1492[1]
	24 Week	10.73 (2.09) 113 10.64 (6.24, 15.50)	10.83 (2.44) 117 10.39 (5.01, 19.82)	0.7332[1]
	24 Week Difference From Baseline	-0.44 (2.12) 113 -0.33 (-5.68, 5.64)	0.09 (2.35) 117 -0.14 (-4.65, 8.94)	0.0374[3]
ITT3	Baseline	11.14 (2.31) 113 10.73 (5.40, 17.05)	10.73 (2.09) 117 10.52 (5.29, 16.08)	0.1620[1]
	24 Week	10.75 (2.12) 113 10.47 (5.99, 15.50)	10.83 (2.37) 117 10.41 (4.97, 19.82)	0.7812[1]
	24 Week Difference From Baseline	-0.39 (2.12) 113 -0.31 (-6.10, 5.64)	0.10 (2.44) 117 -0.08 (-4.65, 8.94)	0.0533[3]
ITT4	Baseline	11.14 (2.31) 113 10.73 (5.40, 17.05)	10.75 (2.12) 117 10.52 (5.29, 16.08)	0.1864[1]
	24 Week	10.66 (2.15) 113 10.33 (6.24, 15.79)	10.83 (2.45) 117 10.39 (4.10, 19.82)	0.5746[1]
	24 Week Difference From Baseline	-0.48 (2.23) 113 -0.31 (-6.03, 6.60)	0.08 (2.33) 117 -0.11 (-4.65, 8.94)	0.0328[3]
ITT5	Baseline	11.17 (2.29) 113 10.76 (5.40, 17.05)	10.74 (2.14) 117 10.44 (5.29, 16.08)	0.1397[1]
	24 Week	10.70 (2.14) 113 10.35 (4.78, 15.50)	10.93 (2.32) 117 10.57 (5.01, 19.82)	0.4334[1]
	24 Week Difference From Baseline	-0.47 (2.03) 113 -0.27 (-5.17, 5.64)	0.20 (2.31) 117 -0.07 (-4.65, 8.94)	**0.0106**[3]
ITT6	Baseline	11.14 (2.31) 113 10.73 (5.40, 17.05)	10.74 (2.10) 117 10.44 (5.29, 16.08)	0.1726[1]
	24 Week	10.61 (2.12) 113 10.47 (6.24, 15.50)	10.82 (2.52) 117 10.39 (4.10, 19.82)	0.4933[1]
	24 Week Difference From Baseline	-0.53 (2.10) 113 -0.48 (-5.13, 5.64)	0.08 (2.38) 117 -0.11 (-4.65, 8.94)	**0.0203**[3]
ITT7	Baseline	11.14 (2.31) 113 10.73 (5.40, 17.05)	10.77 (2.19) 117 10.44 (5.29, 16.84)	0.2106[1]
	24 Week	10.82 (2.12) 113 10.78 (6.24, 15.50)	10.85 (2.39) 117 10.41 (5.01, 19.82)	0.9161[1]
	24 Week Difference From Baseline	-0.32 (2.14) 113 -0.27 (-5.51, 5.64)	0.08 (2.34) 117 -0.07 (-4.65, 8.94)	0.0876[3]
ITT8	Baseline	11.20 (2.30) 113 10.76 (5.40, 17.05)	10.67 (2.13) 117 10.39 (5.29, 16.08)	0.0736[1]
	24 Week	10.62 (2.15) 113 10.35 (5.37, 15.50)	10.79 (2.50) 117 10.39 (4.22, 19.82)	0.5703[1]
	24 Week Difference From Baseline	-0.58 (2.21) 113 -0.33 (-6.71, 5.85)	0.12 (2.48) 117 -0.14 (-5.36, 8.94)	**0.0124**[3]

Table XII.2a Mean AT at Study Time Points with EF ≥25 at Baseline Continued

Imputation	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
ITT9	Baseline	11.20 (2.30) 113 10.76 (5.40, 17.05)	10.75 (2.14) 117 10.44 (5.29, 16.08)	0.1253[1]
	24 Week	10.68 (2.02) 113 10.53 (6.24, 15.50)	10.91 (2.44) 117 10.42 (5.01, 19.82)	0.4372[4]
	24 Week Difference From Baseline	-0.51 (2.08) 113 -0.38 (-5.04, 5.64)	0.17 (2.39) 117 -0.08 (-4.65, 8.94)	**0.0112**[3]
ITT10	Baseline	11.14 (2.31) 113 10.73 (5.40, 17.05)	10.73 (2.14) 117 10.39 (5.29, 16.08)	0.1648[1]
	24 Week	10.62 (2.14) 113 10.35 (5.92, 15.50)	10.78 (2.38) 117 10.39 (5.01, 19.82)	0.6003[1]
	24 Week Difference From Baseline	-0.52 (2.26) 113 -0.38 (-6.17, 5.64)	0.05 (2.32) 117 -0.14 (-4.65, 8.94)	0.0314[3]

[1]Two-sided equal variance Student's t-test.
[2]One-sided unequal variance Student's t-test
[3]One-sided equal variance Student's t-test

The responder analysis for the 10 imputations appears below.

Table XII.2b Univariate Primary Effectiveness Endpoint Results (≥20% Improvement) for ITT Patients with EF ≥25

Population	Control n/N (%)	Optimizer n/N (%)	P-value[1]
ITT1	9/113 (7.96)	23/117 (19.66)	**0.0083**
ITT2	14/113 (12.39)	23/117 (19.66)	0.0930
ITT3	12/113 (10.62)	24/117 (20.51)	0.0292
ITT4	10/113 (8.85)	24/117 (20.51)	**0.0100**
ITT5	11/113 (9.73)	26/117 (22.22)	**0.0078**
ITT6	10/113 (8.85)	23/117 (19.66)	**0.0151**
ITT7	13/113 (11.50)	23/117 (19.66)	0.0637
ITT8	10/113 (8.85)	25/117 (21.37)	**0.0065**
ITT9	11/113 (9.73)	27/117 (23.08)	**0.0050**
ITT10	14/113 (12.39)	24/117 (20.51)	0.0689

[1]One-sided Fisher's exact test

The combination of the 10 ITT imputations in sub-groups by EF, the resulting z = -1.9432 with a corresponding P-value of 0.0260.

The means for the ITT ten imputations with baseline EF≥25 and NYHA=3 are presented below.

Table XII.3a Mean AT at Study Time Points with EF ≥25 and NYHA=3 at Baseline

Imputation	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
ITT1	Baseline	11.19 (2.19) 97 10.73 (7.22, 16.72)	10.72 (2.11) 109 10.44 (5.29, 16.05)	0.1199[1]
	24 Week	10.70 (2.14) 97 10.47 (4.79, 15.50)	10.98 (2.43) 109 10.57 (5.01, 19.82)	0.3783[1]
	24 Week Difference From Baseline	-0.49 (1.97) 97 -0.38 (-7.29, 4.62)	0.27 (2.51) 109 -0.02 (-4.65, 9.17)	**0.0086**[2]
ITT2	Baseline	11.22 (2.17) 97 10.76 (7.22, 16.72)	10.71 (2.17) 109 10.44 (5.29, 16.09)	0.0916[1]
	24 Week	10.77 (2.11) 97 10.53 (6.24, 15.50)	10.89 (2.48) 109 10.42 (5.01, 19.82)	0.7109[1]
	24 Week Difference From Baseline	-0.45 (2.06) 97 -0.38 (-5.68, 4.62)	0.18 (2.38) 109 -0.08 (-4.65, 8.94)	**0.0218**[3]
ITT3	Baseline	11.19 (2.19) 97 10.73 (7.22, 16.72)	10.68 (2.07) 109 10.44 (5.29, 16.05)	0.0884[1]
	24 Week	10.76 (2.18) 97 10.33 (5.99, 15.50)	10.84 (2.41) 109 10.42 (4.97, 19.82)	0.8043[1]
	24 Week Difference From Baseline	-0.42 (2.11) 97 -0.31 (-6.10, 4.62)	0.16 (2.45) 109 -0.02 (-4.65, 8.94)	0.0336[3]
ITT4	Baseline	11.19 (2.19) 97 10.73 (7.22, 16.72)	10.70 (2.11) 109 10.44 (5.29, 16.05)	0.1067[1]
	24 Week	10.76 (2.16) 97 10.35 (6.24, 15.79)	10.85 (2.51) 109 10.42 (4.10, 19.82)	0.7673[1]
	24 Week Difference From Baseline	-0.43 (2.16) 97 -0.27 (-6.03, 6.60)	0.15 (2.38) 109 -0.07 (-4.65, 8.94)	0.0344[3]
ITT5	Baseline	11.22 (2.17) 97 10.76 (7.22, 16.72)	10.69 (2.13) 109 10.39 (5.29, 16.05)	0.0779[1]
	24 Week	10.77 (2.10) 97 10.35 (6.24, 15.50)	10.93 (2.37) 109 10.62 (5.01, 19.82)	0.5946[1]
	24 Week Difference From Baseline	-0.45 (1.92) 97 -0.31 (-5.17, 4.62)	0.24 (2.34) 109 -0.02 (-4.65, 8.94)	**0.0099**[2]
ITT6	Baseline	11.19 (2.19) 97 10.73 (7.22, 16.72)	10.70 (2.09) 109 10.44 (5.29, 16.05)	0.1075[1]
	24 Week	10.65 (2.10) 97 10.35 (6.24, 15.50)	10.83 (2.58) 109 10.41 (4.10, 19.82)	0.5872[4]
	24 Week Difference From Baseline	-0.54 (2.08) 97 -0.49 (-5.13, 5.36)	0.12 (2.42) 109 -0.08 (-4.65, 8.94)	**0.0189**[3]
ITT7	Baseline	11.19 (2.19) 97 10.73 (7.22, 16.72)	10.74 (2.17) 109 10.44 (5.29, 16.84)	0.1452[1]
	24 Week	10.81 (2.12) 97 10.82 (6.24, 15.50)	10.87 (2.41) 109 10.42 (5.01, 19.82)	0.8703[1]
	24 Week Difference From Baseline	-0.37 (2.14) 97 -0.30 (-5.51, 5.11)	0.13 (2.34) 109 -0.02 (-4.65, 8.94)	0.0578[3]
ITT8	Baseline	11.25 (2.19) 97 10.76 (7.22, 16.72)	10.64 (2.10) 109 10.39 (5.29, 16.05)	0.0430[1]
	24 Week	10.66 (2.16) 97 10.35 (5.37, 15.50)	10.79 (2.50) 109 10.41 (4.22, 19.82)	0.6915[1]
	24 Week Difference From Baseline	-0.59 (2.19) 97 -0.33 (-6.71, 5.85)	0.14 (2.44) 109 -0.11 (-5.36, 8.94)	**0.0121**[3]

Table XII.3a Mean AT at Study Time Points with EF ≥25 and NYHA=3 at Baseline (Continued)

Imputation	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
ITT9	Baseline	11.25 (2.19) 97 10.76 (7.22, 16.72)	10.72 (2.11) 109 10.44 (5.29, 16.05)	0.0799[1]
	24 Week	10.73 (2.02) 97 10.47 (6.24, 15.50)	10.91 (2.48) 109 10.50 (5.01, 19.82)	0.5810[4]
	24 Week Difference From Baseline	-0.52 (1.98) 97 -0.48 (-5.04, 5.11)	0.18 (2.43) 109 -0.08 (-4.65, 8.94)	**0.0118**[2]
ITT10	Baseline	11.19 (2.19) 97 10.73 (7.22, 16.72)	10.70 (2.12) 109 10.39 (5.29, 16.05)	0.1106[1]
	24 Week	10.66 (2.14) 97 10.30 (6.24, 15.50)	10.83 (2.42) 109 10.42 (5.01, 19.82)	0.5917[1]
	24 Week Difference From Baseline	-0.53 (2.21) 97 -0.48 (-6.17, 5.50)	0.12 (2.36) 109 -0.08 (-4.65, 8.94)	**0.0213**[3]

[1]Two-sided equal variance Student's t-test.
[2]One-sided unequal variance Student's t-test
[3]One-sided equal variance Student's t-test
[4]Two-sided unequal variance Student's t-test.

The responder analysis for the 10 imputations appears below.

Table XII.3b Univariate Primary Effectiveness Endpoint Results (≥20% Improvement) for ITT Patients with EF ≥25 and NYHA=3 at Baseline

Population	Control n/N (%)	Optimizer n/N (%)	P-value[1]
ITT1	7/97 (7.22)	23/109 (21.10)	**0.0037**
ITT2	11/97 (11.34)	23/109 (21.10)	0.0440
ITT3	10/97 (10.31)	23/109 (21.10)	0.0265
ITT4	8/97 (8.25)	24/109 (22.02)	**0.0050**
ITT5	9/97 (9.28)	25/109 (22.94)	**0.0065**
ITT6	8/97 (8.25)	22/109 (20.18)	**0.0120**
ITT7	11/97 (11.34)	22/109 (20.18)	0.0613
ITT8	8/97 (8.25)	23/109 (21.10)	**0.0078**
ITT9	8/97 (8.25)	25/109 (22.94)	**0.0032**
ITT10	11/97 (11.34)	24/109 (22.02)	0.0311

[1]One-sided Fisher's exact test

Combining the sub-groups from the ten imputations for EF ≥ 25 with NYHA=3 we get a z = -2.2624 with at corresponding P-value of 0.0118.

For the FASA population, the ten imputations for the whole population, EF ≥ 25, and EF ≥ 25 with NYHA=3 are presented in the tables below. The means are presented in the table below.

Table XII.4a Mean AT at Study Time Points

Imputation	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
FASA1	Baseline	10.90 (2.29) 212 10.60 (4.10, 17.05)	10.90 (2.33) 208 10.62 (4.10, 16.92)	0.9798[1]
	24 Week[3]	10.75 (2.27) 212 10.79 (4.10, 19.61)	10.81 (2.46) 207 10.40 (4.10, 19.82)	0.7763[1]
	24 Week Difference From Baseline	-0.15 (2.26) 212 -0.20 (-7.29, 9.34)	-0.08 (2.38) 208 -0.12 (-6.91, 9.17)	0.3784[2]
FASA2	Baseline	10.90 (2.27) 212 10.69 (4.10, 17.05)	10.89 (2.36) 208 10.60 (4.10, 16.92)	0.9516[1]
	24 Week[3]	10.74 (2.25) 212 10.73 (4.10, 19.61)	10.80 (2.51) 207 10.41 (4.10, 19.82)	0.8209[1]
	24 Week Difference From Baseline	-0.16 (2.25) 212 -0.20 (-5.68, 9.34)	-0.10 (2.32) 208 -0.14 (-6.55, 8.94)	0.3936[2]
FASA3	Baseline	10.92 (2.29) 212 10.72 (4.10, 17.05)	10.90 (2.32) 208 10.72 (4.10, 16.92)	0.9138[1]
	24 Week[3]	10.80 (2.29) 212 10.62 (4.10, 19.61)	10.81 (2.48) 207 10.42 (4.10, 19.82)	0.9686[1]
	24 Week Difference From Baseline	-0.12 (2.28) 212 -0.20 (-6.10, 9.34)	-0.09 (2.32) 208 -0.10 (-6.47, 8.94)	0.4404[2]
FASA4	Baseline	10.91 (2.27) 212 10.73 (4.10, 17.05)	10.90 (2.31) 208 10.60 (4.10, 16.92)	0.9661[1]
	24 Week[3]	10.72 (2.30) 212 10.57 (4.10, 19.61)	10.81 (2.50) 207 10.42 (4.10, 19.82)	0.7222[1]
	24 Week Difference From Baseline	-0.19 (2.28) 212 -0.13 (-6.03, 9.34)	-0.10 (2.34) 208 -0.12 (-6.47, 8.94)	0.3447[2]
FASA5	Baseline	10.94 (2.28) 212 10.73 (4.10, 17.05)	10.92 (2.31) 208 10.61 (4.10, 16.92)	0.9293[1]
	24 Week[3]	10.70 (2.31) 212 10.57 (4.10, 19.61)	10.82 (2.44) 207 10.49 (4.10, 19.82)	0.6161[1]
	24 Week Difference From Baseline	-0.24 (2.20) 212 -0.15 (-8.59, 9.34)	-0.11 (2.29) 208 -0.14 (-6.88, 8.94)	0.2778[2]
FASA6	Baseline	10.90 (2.27) 212 10.69 (4.10, 17.05)	10.89 (2.31) 208 10.59 (4.10, 16.92)	0.9437[1]
	24 Week[3]	10.70 (2.28) 212 10.67 (4.10, 19.61)	10.74 (2.55) 207 10.39 (4.10, 19.82)	0.8434[1]
	24 Week Difference From Baseline	-0.21 (2.23) 212 -0.20 (-5.13, 9.34)	-0.15 (2.44) 208 -0.14 (-8.23, 8.94)	0.4052[2]
FASA7	Baseline	10.89 (2.31) 212 10.69(4.10, 17.05)	10.91 (2.34) 208 10.66 (4.10, 16.92)	0.9239[1]
	24 Week[3]	10.82 (2.29) 212 10.81 (4.10, 19.61)	10.78 (2.48) 207 10.40 (4.10, 19.82)	0.8756[1]
	24 Week Difference From Baseline	-0.07 (2.32) 212 -0.11 (-6.65, 9.34)	-0.13 (2.36) 208 -0.10 (-7.99, 8.94)	0.6140[2]
FASA8	Baseline	10.95 (2.28) 212 10.74 (4.10, 17.05)	10.86 (2.34) 208 10.60 (4.10, 16.92)	0.6683[1]
	24 Week[3]	10.68 (2.28) 212 10.56 (4.10, 19.61)	10.71 (2.51) 207 10.38 (4.10, 19.82)	0.9027[1]
	24 Week Difference From Baseline	-0.27 (2.23) 212 -0.23 (-6.71, 9.34)	-0.15 (2.43) 208 -0.17 (-6.91, 8.94)	0.2947[2]

Table XII.4a Mean AT at Study Time Points (Continued)

Imputation	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
FASA9	Baseline	10.94 (2.28) 212 10.73 (4.10, 17.05)	10.91 (2.32) 208 10.60 (4.10, 16.92)	0.8806[1]
	24 Week[3]	10.72 (2.22) 212 10.73 (4.10, 19.61)	10.83 (2.52) 207 10.41 (4.10, 19.82)	0.6582[1]
	24 Week Difference From Baseline	-0.22 (2.15) 212 -0.23 (-5.04, 9.34)	-0.08 (2.29) 208 -0.15 (-6.51, 8.94)	0.2612[2]
FASA10	Baseline	10.90 (2.28) 212 10.60 (4.10, 17.05)	10.91 (2.30) 208 10.59 (4.10, 16.92)	0.9748[1]
	24 Week[3]	10.69 (2.33) 212 10.67 (4.10, 19.61)	10.79 (2.46) 207 10.42 (4.10, 19.82)	0.6820[1]
	24 Week Difference From Baseline	-0.21 (2.34) 212 -0.15 (-8.59, 9.34)	-0.11 (2.23) 208 -0.24 (-6.47, 8.94)	0.3337[2]

[1]Two-sided equal variance Student's t-test.
[2]One-sided equal variance Student's t-test
[3]One patient in the Optimizer group had a difference imputed but did not have a 24 week AT imputed.

The responder analysis for the 10 imputations appears below.

Table XII.4b Univariate Primary Effectiveness Endpoint Results (≥20% Improvement) for FASA Patients

Population	Control n/N (%)	Optimizer n/N (%)	P-value[1]
FASA1	28/212 (13.21)	37/208 (17.79)	0.1224
FASA2	31/212 (14.62)	35/208 (16.83)	0.3133
FASA3	29/212 (13.68)	37/208 (17.79)	0.1532
FASA4	26/212 (12.26)	37/208 (17.79)	0.0736
FASA5	27/212 (12.74)	39/208 (18.75)	0.0593
FASA6	26/212 (12.26)	35/208 (16.83)	0.1173
FASA7	30/212 (14.15)	36/208 (17.31)	0.2253
FASA8	24/212 (11.32)	38/208 (18.27)	0.0305
FASA9	27/212 (12.74)	39/208 (18.75)	0.0593
FASA10	33/212 (15.57)	36/208 (17.31)	0.3632

[1]One-sided Fisher's exact test

The combined imputations for the FASA patients resulted in a z = -0.4745 with a corresponding P=0.3176.

The means for the FASA ten imputations with baseline EF≥25 are presented below.

Table XII.5a Mean AT at Study Time Points with EF ≥25 at Baseline

Imputation	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
FASA1	Baseline	11.16 (2.31) 112 10.74 (5.40, 17.05)	10.73 (2.13) 112 10.42 (5.29, 16.08)	0.1485[1]
	24 Week	10.70 (2.09) 112 10.71 (4.79, 15.50)	10.92 (2.41) 112 10.42 (5.01, 19.82)	0.4626[1]
	24 Week Difference From Baseline	-0.45 (2.03) 112 -0.36 (-7.29, 5.64)	0.20 (2.49) 112 -0.08 (-4.65, 9.17)	0.0163[2]
FASA2	Baseline	11.19 (2.29) 112 10.79 (5.40, 17.05)	10.74 (2.21) 112 10.42 (5.29, 16.09)	0.1429[1]
	24 Week	10.74 (2.10) 112 10.71 (6.24, 15.50)	10.82 (2.48) 112 10.37 (5.01, 19.82)	0.7973[1]
	24 Week Difference From Baseline	-0.44 (2.13) 112 -0.36 (-5.68, 5.64)	0.08 (2.40) 112 -0.15(-4.65, 8.94)	0.0434[3]
FASA3	Baseline	11.16 (2.31) 112 10.74 (5.40, 17.05)	10.73 (2.12) 112 10.48 (5.29, 16.08)	0.1546[1]
	24 Week	10.76 (2.13) 112 10.49 (5.99, 15.50)	10.84 (2.41) 112 10.42 (4.97, 19.82)	0.7878[1]
	24 Week Difference From Baseline	-0.40 (2.13) 112 -0.32 (-6.10, 5.64)	0.11 (2.47) 112 -0.09(-4.65, 8.94)	0.0512[3]
FASA4	Baseline	11.16 (2.31) 112 10.74 (5.40, 17.05)	10.74 (2.14) 112 10.48 (5.29, 16.08)	0.1626[1]
	24 Week	10.67 (2.16) 112 10.34 (6.24, 15.79)	10.83 (2.43) 112 10.40 (4.10, 19.82)	0.6130[1]
	24 Week Difference From Baseline	-0.49 (2.24) 112 -0.32 (-6.03, 6.60)	0.09 (2.33) 112 -0.12(-4.65, 8.94)	0.0314[3]
FASA5	Baseline	11.19 (2.29) 112 10.79 (5.40, 17.05)	10.75 (2.17) 112 10.48 (5.29, 16.08)	0.1436[1]
	24 Week	10.71 (2.14) 112 10.41 (4.78, 15.50)	10.91 (2.35) 112 10.46 (5.01, 19.82)	0.5038[1]
	24 Week Difference From Baseline	-0.47 (2.03) 112 -0.29 (-5.17, 5.64)	0.17 (2.32) 112 -0.09(-4.65, 8.94)	0.0148[3]
FASA6	Baseline	11.16 (2.31) 112 10.74 (5.40, 17.05)	10.73 (2.13) 112 10.42 (5.29, 16.08)	0.1499[1]
	24 Week	10.62 (2.13) 112 10.50 (6.24, 15.50)	10.79 (2.51) 112 10.37 (4.10, 19.82)	0.5921[1]
	24 Week Difference From Baseline	-0.54 (2.11) 112 -0.49 (-5.13, 5.64)	0.06 (2.40) 112 -0.12 (-4.65, 8.94)	0.0250[3]
FASA7	Baseline	11.16 (2.31) 112 10.74 (5.40, 17.05)	10.74 (2.20) 112 10.42 (5.29, 16.84)	0.1693[1]
	24 Week	10.83 (2.13) 112 10.80 (6.24, 15.50)	10.82 (2.41) 112 10.37 (5.01, 19.82)	0.9757[1]
	24 Week Difference From Baseline	-0.32 (2.15) 112 -0.28 (-5.51, 5.64)	0.08 (2.38) 112 -0.09 (-4.65, 8.94)	0.0908[3]
FASA8	Baseline	11.21 (2.31) 112 10.79 (5.40, 17.05)	10.68 (2.15) 112 10.42 (5.29, 16.08)	0.0764[1]
	24 Week	10.63 (2.16) 112 10.41 (5.37, 15.50)	10.80 (2.53) 112 10.37 (4.22, 19.82)	0.5992[1]
	24 Week Difference From Baseline	-0.58 (2.22) 112 -0.33 (-6.71, 5.85)	0.11 (2.53) 112 -0.15 (-5.36, 8.94)	0.0148[3]

Table XII.5a Mean AT at Study Time Points with EF ≥25 at Baseline

Imputation	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
FASA9	Baseline	11.21 (2.31) 112 10.79 (5.40, 17.05)	10.74 (2.17) 112 10.42 (5.29, 16.08)	0.1130[1]
	24 Week	10.70 (2.02) 112 10.58 (6.24, 15.50)	10.92 (2.47) 112 10.42 (5.01, 19.82)	0.4599[4]
	24 Week Difference From Baseline	-0.52 (2.09) 112 -0.43 (-5.04, 5.64)	0.18 (2.41) 112 -0.09 (-4.65, 8.94)	0.0106[2]
FASA10	Baseline	11.16 (2.31) 112 10.74 (5.40, 17.05)	10.74 (2.17) 112 10.42 (5.29, 16.08)	0.1687[1]
	24 Week	10.64 (2.14) 112 10.39 (5.92, 15.50)	10.78 (2.40) 112 10.39 (5.01, 19.82)	0.6452[1]
	24 Week Difference From Baseline	-0.52 (2.27) 112 -0.43 (-6.17, 5.64)	0.03 (2.31) 112 -0.16(-4.65, 8.94)	0.0358[3]

[1]Two-sided equal variance Student's t-test.
[2]One-sided unequal variance Student's t-test
[3]One-sided equal variance Student's t-test
[4]Two-sided unequal variance Student's t-test

The responder analysis for the 10 imputations appears below.

Table XII.5b Univariate Primary Effectiveness Endpoint Results (≥20% Improvement) for FASA Patients with EF ≥25

Population	Control n/N (%)	Optimizer n/N (%)	P-value[1]
FASA1	9/112 (8.04)	23/112 (20.54)	**0.0061**
FASA2	14/112 (12.50)	22/112 (19.64)	0.1012
FASA3	12/112 (10.71)	23/112 (20.54)	0.0323
FASA4	10/112 (8.93)	23/112 (20.54)	**0.0113**
FASA5	11/112 (9.82)	25/112 (22.32)	**0. 0086**
FASA6	10/112 (8.93)	22/112 (19.64)	**0.0172**
FASA7	13/112 (11.61)	23/112 (20.54)	0. 0503
FASA8	10/112 (8.93)	24/112 (21.43)	**0. 0073**
FASA9	11/112 (9.82)	26/112 (23.21)	**0. 0055**
FASA10	14/112 (12.50)	23/112 (20.54)	0. 0747

[1]One-sided Fisher's exact test

Combining these ten imputations for EF≥25 a z = -1.9292 with a P-value of 0.0269.

The means for the FASA ten imputations with baseline EF≥25 and NYHA=3 are presented below.

Table XII.6a Mean AT at Study Time Points with EF ≥25 and NYHA=3 at Baseline

Imputation	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
FASA1	Baseline	11.21 (2.19) 96 10.74 (7.22, 16.72)	10.68 (2.11) 104 10.42 (5.29, 16.05)	0. 0877[1]
	24 Week	10.72 (2.14) 96 10.50 (4.79, 15.50)	10.96 (2.46) 104 10.46 (5.01, 19.82)	0. 4646[1]
	24 Week Difference From Baseline	-0.49 (1.98) 96 -0.40 (-7.29, 4.62)	0.27 (2.56) 104 -0.01 (-4.65, 9.17)	0.0094[2]
FASA2	Baseline	11.24 (2.17) 96 10.79 (7.22, 16.72)	10.71 (2.20) 104 10.42 (5.29, 16.09)	0. 0861[1]
	24 Week	10.78 (2.11) 96 10.67 (6.24, 15.50)	10.88 (2.52) 104 10.42 (5.01, 19.82)	0. 7729[1]
	24 Week Difference From Baseline	-0.46 (2.07) 96 -0.43 (-5.68, 4.62)	0.17 (2.43) 104 -0.09 (-4.65, 8.94)	0.0251[3]
FASA3	Baseline	11.21 (2.19) 96 10.74 (7.22, 16.72)	10.68 (2.10) 104 10.42 (5.29, 16.05)	0. 0822[1]
	24 Week	10.78 (2.18) 96 10.34 (5.99, 15.50)	10.86 (2.44) 104 10.46 (4.97, 19.82)	0.8127[1]
	24 Week Difference From Baseline	-0.43 (2.12) 96 -0.35 (-6.10, 4.62)	0.18 (2.49) 104 -0.05 (-4.65, 8.94)	0.0322[3]
FASA4	Baseline	11.21 (2.19) 96 10.74 (7.22, 16.72)	10.68 (2.13) 104 10.42 (5.29, 16.05)	0.0892[1]
	24 Week	10.77 (2.17) 96 10.39 (6.24, 15.79)	10.85 (2.50) 104 10.46 (4.10, 19.82)	0.8106[1]
	24 Week Difference From Baseline	-0.43 (2.17) 96 -0.29 (-6.03, 6.60)	0.17 (2.39) 104 -0.07 (-4.65, 8.94)	0.0322[3]
FASA5	Baseline	11.24 (2.17) 96 10.79 (7.22, 16.72)	10.70 (2.16) 104 10.42 (5.29, 16.05)	0.0791[1]
	24 Week	10.78 (2.10) 96 10.41 (6.24, 15.50)	10.91 (2.40) 104 10.53 (5.01, 19.82)	0.6785[1]
	24 Week Difference From Baseline	-0.46 (1.93) 96 -0.34 (-5.17, 4.62)	0.21 (2.35) 104 -0.05 (-4.65, 8.94)	0.0145[3]
FASA6	Baseline	11.21 (2.19) 96 10.74 (7.22, 16.72)	10.69 (2.11) 104 10.42 (5.29, 16.05)	0.0897[1]
	24 Week	10.66 (2.11) 96 10.41 (6.24, 15.50)	10.79 (2.57) 104 10.40 (4.10, 19.82)	0.7010[1]
	24 Week Difference From Baseline	-0.54 (2.09) 96 -0.49 (-5.13, 5.36)	0.10 (2.44) 104 -0.09 (-4.65, 9.17)	0.0227[3]
FASA7	Baseline	11.21 (2.20) 96 10.74 (7.22, 16.72)	10.71 (2.18) 104 10.42 (5.29, 16.09)	0.1113[1]
	24 Week	10.83 (2.13) 96 10.83 (6.24, 15.50)	10.84 (2.43) 104 10.40 (5.01, 19.82)	0.9810[1]
	24 Week Difference From Baseline	-0.38 (2.16) 96 -0.30 (-5.51, 5.11)	0.13 (2.38) 104 -0.07 (-4.65, 8.94)	0.0602[3]
FASA8	Baseline	11.27 (2.19) 96 10.79 (7.22, 16.72)	10.66 (2.13) 104 10.42 (5.29, 16.05)	0.0442[1]
	24 Week	10.67 (2.17) 96 10.41 (5.37, 15.50)	10.79 (2.53) 104 10.40 (4.22, 19.82)	0.7252[1]
	24 Week Difference From Baseline	-0.60 (2.20) 96 -0.35 (-6.71, 5.85)	0.14 (2.49) 104 -0.12 (-5.36, 8.94)	0.0145[3]

Table XII.6a Mean AT at Study Time Points with EF ≥25 and NYHA=3 at Baseline (Continued)

Imputation	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
FASA9	Baseline	11.27 (2.19) 96 10.79 (7.22, 16.72)	10.72 (2.14) 104 10.42 (5.29, 16.05)	0.0702[1]
	24 Week	10.75 (2.02) 96 10.50 (6.24, 15.50)	10.91 (2.51) 104 10.46 (5.01, 19.82)	0.6090[4]
	24 Week Difference From Baseline	-0.53 (1.99) 96 -0.49 (-5.04, 5.11)	0.20 (2.46) 104 -0.09 (-4.65, 8.94)	0.0121[2]
FASA10	Baseline	11.21 (2.20) 96 10.74 (7.22, 16.72)	10.72 (2.14) 104 10.42 (5.29, 16.05)	0.1122[1]
	24 Week	10.67 (2.15) 96 10.32 (6.24, 15.50)	10.83 (2.44) 104 10.42 (5.01, 19.82)	0.6355[1]
	24 Week Difference From Baseline	-0.54 (2.22) 96 -0.49 (-6.17, 5.50)	0.11 (2.35) 104 -0.12 (-4.65, 8.94)	0.0240[2]

[1]Two-sided equal variance Student's t-test.
[2]One-sided unequal variance Student's t-test
[3]One-sided equal variance Student's t-test
[4]Two-sided unequal variance Student's t-test.

The responder analysis for the 10 imputations appears below.

Table XII.6b Univariate Primary Effectiveness Endpoint Results (≥20% Improvement) for FASA Patients with EF ≥25 and NYHA=3 at Baseline

Population	Control n/N (%)	Optimizer n/N (%)	P-value[1]
FASA1	7/96 (7.29)	23/104 (22.12)	**0.0027**
FASA2	11/96 (11.46)	22/104 (21.15)	0.0481
FASA3	10/96 (10.42)	22/104 (21.15)	0.0294
FASA4	8/96 (8.33)	23/104 (22.12)	**0.0057**
FASA5	9/96 (9.38)	24/104 (23.08)	**0.0072**
FASA6	8/96 (8.33)	21/104 (20.19)	**0.0137**
FASA7	11/96 (11.46)	22/104 (21.15)	0.0481
FASA8	8/96 (8.33)	22/104 (21.15)	**0.0089**
FASA9	8/96 (8.33)	24/104 (23.08)	**0.0036**
FASA10	11/96 (11.46)	23/104 (22.12)	0.0338

[1]One-sided Fisher's exact test

The combination of the 10 imputations for the sub-group of FASA EF≥25 and NYHA=3 yields a z = -2.2512 with a P = 0.0121.

For the FASB population, the ten imputations for the whole population, EF ≥ 25, and EF ≥ 25 with NYHA=3 are presented in the tables below. The means are presented in the table below.

Table XII.7a Mean AT at Study Time Points

Imputation	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
FASB1	Baseline	10.87 (2.30) 207 10.54 (4.10, 17.05)	10.90 (2.33) 208 10.62 (4.10, 16.92)	0.8975[1]
	24 Week[3]	10.74 (2.27) 207 10.78 (4.10, 19.61)	10.81 (2.46) 207 10.40 (4.10, 19.82)	0.7419[1]
	24 Week Difference From Baseline	-0.13 (2.23) 207 -0.17 (-7.29, 9.34)	-0.08 (2.38) 208 -0.12 (-6.91, 9.17)	0.4208[2]
FASB2	Baseline	10.87 (2.28) 207 10.56 (4.10, 17.05)	10.89 (2.36) 208 10.60 (4.10, 16.92)	0.9257[1]
	24 Week[3]	10.76 (2.26) 207 10.78 (4.10, 19.61)	10.80 (2.51) 207 10.41 (4.10, 19.82)	0.8944[1]
	24 Week Difference From Baseline	-0.11 (2.24) 207 -0.12 (-5.68, 9.34)	-0.10 (2.32) 208 -0.14 (-6.55, 8.94)	0.4920[2]
FASB3	Baseline	10.89 (2.30) 207 10.65 (4.10, 17.05)	10.90 (2.32) 208 10.72 (4.10, 16.92)	0.9642[1]
	24 Week[3]	10.80 (2.28) 207 10.64 (4.10, 19.61)	10.81 (2.48) 207 10.42 (4.10, 19.82)	0.9533[1]
	24 Week Difference From Baseline	-0.09 (2.22) 207 -0.17 (-6.10, 9.34)	-0.09 (2.32) 208 -0.10 (-6.47, 8.94)	0.4920[2]
FASB4	Baseline	10.87 (2.28) 207 10.65 (4.10, 17.05)	10.90 (2.31) 208 10.60 (4.10, 16.92)	0.9105[1]
	24 Week[3]	10.72 (2.32) 207 10.53 (4.10, 19.61)	10.81 (2.50) 207 10.42 (4.10, 19.82)	0.7024[1]
	24 Week Difference From Baseline	-0.16 (2.27) 207 -0.13 (-6.03, 9.34)	-0.10 (2.34) 208 -0.12 (-6.47, 8.94)	0.3936[2]
FASB5	Baseline	10.91 (2.29) 207 10.65 (4.10, 17.05)	10.92 (2.31) 208 10.61 (4.10, 16.92)	0.9500[1]
	24 Week[3]	10.73 (2.28) 207 10.61 (4.10, 19.61)	10.82 (2.44) 207 10.49 (4.10, 19.82)	0.6993[1]
	24 Week Difference From Baseline	-0.18 (2.10) 207 -0.13 (-5.17, 9.34)	-0.11 (2.29) 208 -0.14 (-6.88, 8.94)	0.3746[2]
FASB6	Baseline	10.87 (2.28) 207 10.56 (4.10, 17.05)	10.89 (2.31) 208 10.59 (4.10, 16.92)	0.9319[1]
	24 Week[3]	10.70 (2.30) 207 10.70 (4.10, 19.61)	10.74 (2.55) 207 10.39 (4.10, 19.82)	0.8646[1]
	24 Week Difference From Baseline	-0.17 (2.23) 207 -0.13 (-5.13, 9.34)	-0.15 (2.44) 208 -0.14 (-8.23, 8.94)	0.4761[2]
FASB7	Baseline	10.85 (2.31) 207 10.56 (4.10, 17.05)	10.91 (2.34) 208 10.66 (4.10, 16.92)	0.8030[1]
	24 Week[3]	10.81 (2.28) 207 10.80 (4.10, 19.61)	10.78 (2.48) 207 10.40 (4.10, 19.82)	0.8936[1]
	24 Week Difference From Baseline	-0.04 (2.30) 207 -0.10 (-6.65, 9.34)	-0.13 (2.36) 208 -0.10 (-7.99, 8.94)	0.6626[2]
FASB8	Baseline	10.92 (2.29) 207 10.73 (4.10, 17.05)	10.86 (2.34) 208 10.60 (4.10, 16.92)	0.7820[1]
	24 Week[3]	10.71 (2.29) 207 10.61 (4.10, 19.61)	10.71 (2.51) 207 10.38 (4.10, 19.82)	0.9986[1]
	24 Week Difference From Baseline	-0.21 (2.20) 207 -0.17 (-6.71, 9.34)	-0.15 (2.43) 208 -0.17 (-6.91, 8.94)	0.3936[2]

Table XII.7a Mean AT at Study Time Points (Continued)

Imputation	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
FASB9	Baseline	10.91 (2.29) 207 10.65 (4.10, 17.05)	10.91 (2.32) 208 10.60 (4.10, 16.92)	0.9991[1]
	24 Week[3]	10.72 (2.23) 207 10.72 (4.10, 19.61)	10.83 (2.52) 207 10.41 (4.10, 19.82)	0.6395[1]
	24 Week Difference From Baseline	-0.19 (2.14) 207 -0.23 (-5.04, 9.34)	-0.08 (2.29) 208 -0.15 (-6.51, 8.94)	0.3052[2]
FASB10	Baseline	10.87 (2.29) 207 10.54 (4.10, 17.05)	10.91 (2.30) 208 10.59 (4.10, 16.92)	0.8522[1]
	24 Week[3]	10.76 (2.29) 207 10.72 (4.10, 19.61)	10.79 (2.46) 207 10.42 (4.10, 19.82)	0.8981[1]
	24 Week Difference From Baseline	-0.11 (2.22) 207 -0.12 (-6.03, 9.34)	-0.11 (2.23) 208 -0.24 (-6.47, 8.94)	0.5079[2]

[1]Two-sided equal variance Student's t-test.
[2]One-sided equal variance Student's t-test
[3]One patient in the Optimizer group had a difference imputed but did not have a 24 week AT imputed.

The responder analysis for the 10 imputations appears below.

Table XII.7b Univariate Primary Effectiveness Endpoint Results (≥20% Improvement) for FASB Patients

Population	Control n/N (%)	Optimizer n/N (%)	P-value[1]
FASB1	27/207 (13.04)	37/208 (17.79)	0.1145
FASB2	31/207 (14.98)	35/208 (16.83)	0.3516
FASB3	28/207 (13.53)	37/208 (17.79)	0.1447
FASB4	26/207 (12.56)	37/208 (17.79)	0.0888
FASB5	27/207 (13.04)	39/208 (18.75)	0.0726
FASB6	26/207 (12.56)	35/208 (16.83)	0.1381
FASB7	30/207 (14.49)	36/208 (17.31)	0.2580
FASB8	24/207 (11.59)	38/208 (18.27)	0.0381
FASB9	27/207 (13.04)	39/208 (18.75)	0.0726
FASB10	30/207 (15.94)	36/208 (17.31)	0.4046

[1]One-sided Fisher's exact test

The total FASB population results in a combined z = -0.4959 with corresponding P-value of 0.3100.

The means for the FASB ten imputations with baseline EF≥25 are presented below.

Table XII.8a Mean AT at Study Time Points with EF ≥25 at Baseline

Imputation	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
FASB1	Baseline	11.12 (2.33) 108 10.73 (5.40, 17.05)	10.73 (2.13) 112 10.42 (5.29, 16.08)	0.1970[1]
	24 Week	10.65 (2.08) 108 10.58 (4.79, 15.50)	10.92 (2.41) 112 10.42 (5.01, 19.82)	0.3698[1]
	24 Week Difference From Baseline	-0.46 (1.99) 108 -0.36 (-7.29, 5.64)	0.20 (2.49) 112 -0.08 (-4.65, 9.17)	0.0152[2]
FASB2	Baseline	11.15 (2.31) 108 10.74 (5.40, 17.05)	10.74 (2.21) 112 10.42 (5.29, 16.09)	0.1884[1]
	24 Week	10.77 (2.10) 108 10.80 (6.24, 15.50)	10.82 (2.48) 112 10.37 (5.01, 19.82)	0.8676[1]
	24 Week Difference From Baseline	-0.38 (2.12) 108 -0.29 (-5.68, 5.64)	0.08 (2.40) 112 -0.15 (-4.65, 8.94)	0.0688[3]
FASB3	Baseline	11.12 (2.33) 108 10.73 (5.40, 17.05)	10.73 (2.12) 112 10.48 (5.29, 16.08)	0.2045[1]
	24 Week	10.72 (2.11) 108 10.49 (5.99, 15.50)	10.84 (2.41) 112 10.42 (4.97, 19.82)	0.6958[1]
	24 Week Difference From Baseline	-0.39 (2.05) 108 -0.32 (-6.10, 5.64)	0.11 (2.47) 112 -0.09 (-4.65, 8.94)	0.0512[3]
FASB4	Baseline	11.12 (2.33) 108 10.73 (5.40, 17.05)	10.74 (2.14) 112 10.48 (5.29, 16.08)	0.2139[1]
	24 Week	10.68 (2.19) 108 10.34 (6.24, 15.79)	10.83 (2.43) 112 10.40 (4.10, 19.82)	0.6299[1]
	24 Week Difference From Baseline	-0.44 (2.23) 108 -0.32 (-6.03, 6.60)	0.09 (2.33) 112 -0.12 (-4.65, 8.94)	0.0443[3]
FASB5	Baseline	11.15 (2.31) 108 10.74 (5.40, 17.05)	10.75 (2.17) 112 10.48 (5.29, 16.08)	0.1896[1]
	24 Week	10.70 (2.16) 108 10.41 (4.78, 15.50)	10.91 (2.35) 112 10.46 (5.01, 19.82)	0.4895[1]
	24 Week Difference From Baseline	-0.44 (1.99) 108 -0.29 (-5.17, 5.64)	0.17 (2.32) 112 -0.09 (-4.65, 8.94)	0.0193[3]
FASB6	Baseline	11.12 (2.33) 108 10.73 (5.40, 17.05)	10.73 (2.13) 112 10.42 (5.29, 16.08)	0.1986[1]
	24 Week	10.62 (2.16) 108 10.50 (6.24, 15.50)	10.79 (2.51) 112 10.37 (4.10, 19.82)	0.6016[1]
	24 Week Difference From Baseline	-0.49 (2.12) 108 -0.43 (-5.13, 5.64)	0.06 (2.40) 112 -0.12 (-4.65, 8.94)	0.0358[3]
FASB7	Baseline	11.11 (2.33) 108 10.73 (5.40, 17.05)	10.74 (2.20) 112 10.42 (5.29, 16.84)	0.2215[1]
	24 Week	10.80 (2.08) 108 10.77 (6.24, 15.50)	10.82 (2.41) 112 10.37 (5.01, 19.82)	0.9448[1]
	24 Week Difference From Baseline	-0.31 (2.13) 108 -0.28 (-5.51, 5.64)	0.08 (2.38) 112 -0.09 (-4.65, 8.94)	0.0975[3]
FASB8	Baseline	11.17 (2.33) 108 10.74 (5.40, 17.05)	10.68 (2.15) 112 10.42 (5.29, 16.08)	0.1051[1]
	24 Week	10.67 (2.17) 108 10.49 (5.37, 15.50)	10.80 (2.53) 112 10.37 (4.22, 19.82)	0.6907[1]
	24 Week Difference From Baseline	-0.51 (2.18) 108 -0.32 (-6.71, 5.85)	0.11 (2.53) 112 -0.15 (-5.36, 8.94)	0.0268[3]

Table XII.8a Mean AT at Study Time Points with EF ≥25 at Baseline

Imputation	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
FASB9	Baseline	11.17 (2.33) 108 10.74 (5.40, 17.05)	10.74 (2.17) 112 10.42 (5.29, 16.08)	0.1509[1]
	24 Week	10.71 (2.05) 108 10.58 (6.24, 15.50)	10.92 (2.47) 112 10.42 (5.01, 19.82)	0.4928[1]
	24 Week Difference From Baseline	-0.46 (2.07) 108 -0.36 (-5.04, 5.64)	0.18 (2.41) 112 -0.09 (-4.65, 8.94)	0.0171[3]
FASB10	Baseline	11.11 (2.33) 108 10.73 (5.40, 17.05)	10.74 (2.17) 112 10.42 (5.29, 16.08)	0.2211[1]
	24 Week	10.70 (2.13) 108 10.45 (5.92, 15.50)	10.78 (2.40) 112 10.39 (5.01, 19.82)	0.8030[1]
	24 Week Difference From Baseline	-0.42 (2.19) 108 -0.36 (-6.03, 5.64)	0.03 (2.31) 112 -0.16 (-4.65, 8.94)	0.0702[3]

[1]Two-sided equal variance Student's t-test.
[2]One-sided unequal variance Student's t-test
[3]One-sided equal variance Student's t-test

The responder analysis for the 10 imputations appears below.

Table XII.8b Univariate Primary Effectiveness Endpoint Results (≥20% Improvement) for FASB Patients with EF ≥25

Population	Control n/N (%)	Optimizer n/N (%)	P-value[1]
FASB1	8/108 (7.41)	23/112 (20.54)	**0.0041**
FASB2	14/108 (12.96)	22/112 (19.64)	0.1236
FASB3	11/108 (10.19)	23/112 (20.54)	0.0257
FASB4	10/108 (9.26)	23/112 (20.54)	**0.0150**
FASB5	11/108 (10.19)	25/112 (22.32)	**0.0116**
FASB6	10/108 (9.26)	22/112 (19.64)	**0.0224**
FASB7	13/108 (12.04)	23/112 (20.54)	0.0636
FASB8	10/108 (9.26)	24/112 (21.43)	**0.0099**
FASB9	11/108 (10.19)	26/112 (23.21)	**0.0076**
FASB10	14/108 (12.96)	23/112 (20.54)	0.0929

[1]One-sided Fisher's exact test

Combining the ten imputations for FASB (EF≥25), the resulting z = -1.9045 with P-value equal to 0.0284.

The means for the FASB ten imputations with baseline EF≥25 and NYHA=3 are presented below.

Table XII.9a Mean AT at Study Time Points with EF ≥25 and NYHA=3 at Baseline

Imputation	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
FASB1	Baseline	11.18 (2.21) 93 10.73 (7.22, 16.72)	10.68 (2.11) 104 10.42 (5.29, 16.05)	0.1072[1]
	24 Week	10.65 (2.12) 93 10.35 (4.79, 15.50)	10.96 (2.46) 104 10.46 (5.01, 19.82)	0.3446[1]
	24 Week Difference From Baseline	-0.54 (1.95) 93 -0.43 (-7.29, 4.62)	0.27 (2.56) 104 -0.01 (-4.65, 9.17)	0.0065[2]
FASB2	Baseline	11.22 (2.19) 93 10.76 (7.22, 16.72)	10.71 (2.20) 104 10.42 (5.29, 16.09)	0.1043[1]
	24 Week	10.84 (2.12) 93 10.85 (6.24, 15.50)	10.88 (2.52) 104 10.42 (5.01, 19.82)	0.9000[1]
	24 Week Difference From Baseline	-0.38 (2.04) 93 -0.31 (-5.68, 4.62)	0.17 (2.43) 104 -0.09 (-4.65, 8.94)	0.0435[3]
FASB3	Baseline	11.18 (2.21) 93 10.73 (7.22, 16.72)	10.68 (2.10) 104 10.42 (5.29, 16.05)	0.1008[1]
	24 Week	10.73 (2.15) 93 10.33 (5.99, 15.50)	10.86 (2.44) 104 10.46 (4.97, 19.82)	0.6956[1]
	24 Week Difference From Baseline	-0.46 (2.04) 93 -0.38 (-6.10, 4.62)	0.18 (2.49) 104 -0.05 (-4.65, 8.94)	0.0263[3]
FASB4	Baseline	11.18 (2.21) 93 10.73 (7.22, 16.72)	10.68 (2.13) 104 10.42 (5.29, 16.05)	0.1088[1]
	24 Week	10.76 (2.20) 93 10.35 (6.24, 15.79)	10.85 (2.50) 104 10.46 (4.10, 19.82)	0.7906[1]
	24 Week Difference From Baseline	-0.42 (2.17) 93 -0.31 (-6.03, 6.60)	0.17 (2.39) 104 -0.07 (-4.65, 8.94)	0.0367[3]
FASB5	Baseline	11.22 (2.19) 93 10.76 (7.22, 16.72)	10.70 (2.16) 104 10.42 (5.29, 16.05)	0.0965[1]
	24 Week	10.75 (2.11) 93 10.35 (6.24, 15.50)	10.91 (2.40) 104 10.53 (5.01, 19.82)	0.6186[1]
	24 Week Difference From Baseline	-0.46 (1.91) 93 -0.38 (-5.17, 4.62)	0.21 (2.35) 104 -0.05 (-4.65, 8.94)	0.0135[2]
FASB6	Baseline	11.18 (2.21) 93 10.73 (7.22, 16.72)	10.69 (2.11) 104 10.42 (5.29, 16.05)	0.1095[1]
	24 Week	10.66 (2.13) 93 10.35 (6.24, 15.50)	10.79 (2.57) 104 10.40 (4.10, 19.82)	0.6987[4]
	24 Week Difference From Baseline	-0.52 (2.10) 93 -0.49 (-5.13, 5.36)	0.10 (2.44) 104 -0.09 (-4.65, 8.94)	0.0282[3]
FASB7	Baseline	11.18 (2.22) 93 10.73 (7.22, 16.72)	10.71 (2.18) 104 10.42 (5.29, 16.84)	0.1342[1]
	24 Week	10.84 (2.11) 93 10.82 (6.24, 15.50)	10.84 (2.43) 104 10.40 (5.01, 19.82)	0.9966[1]
	24 Week Difference From Baseline	-0.34 (2.13) 93 -0.30 (-5.51, 5.11)	0.13 (2.38) 104 -0.07 (-4.65, 8.94)	0.0743[3]
FASB8	Baseline	11.25 (2.21) 93 10.76 (7.22, 16.72)	10.66 (2.13) 104 10.42 (5.29, 16.05)	0.0550[1]
	24 Week	10.71 (2.17) 93 10.47 (5.37, 15.50)	10.79 (2.53) 104 10.40 (4.22, 19.82)	0.8163[1]
	24 Week Difference From Baseline	-0.54 (2.16) 93 -0.33 (-6.71, 5.85)	0.14 (2.49) 104 -0.12 (-5.36, 8.94)	0.0224[3]

Table XII.9a Mean AT at Study Time Points with EF ≥25 and NYHA=3 at Baseline

Imputation	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
FASB9	Baseline	11.25 (2.21) 93 10.76 (7.22, 16.72)	10.72 (2.14) 104 10.42 (5.29, 16.05)	0.0854[1]
	24 Week	10.74 (2.05) 93 10.47 (6.24, 15.50)	10.91 (2.51) 104 10.46 (5.01, 19.82)	0.6064[4]
	24 Week Difference From Baseline	-0.51 (2.00) 93 -0.48 (-5.04, 5.11)	0.20 (2.46) 104 -0.09 (-4.65, 8.94)	0.0141[2]
FASB10	Baseline	11.18 (2.22) 93 10.73 (7.22, 16.72)	10.72 (2.14) 104 10.42 (5.29, 16.05)	0.1353[1]
	24 Week	10.73 (2.13) 93 10.33 (6.24, 15.50)	10.83 (2.44) 104 10.42 (5.01, 19.82)	0.7643[1]
	24 Week Difference From Baseline	-0.46 (2.15) 93 -0.48 (-6.03, 5.50)	0.11 (2.35) 104 -0.12 (-4.65, 8.94)	0.0408[3]

[1]Two-sided equal variance Student's t-test.
[2]One-sided unequal variance Student's t-test
[3]One-sided equal variance Student's t-test
[4]Two-sided unequal variance Student's t-test.

The responder analysis for the 10 imputations appears below.

Table XII.9b Univariate Primary Effectiveness Endpoint Results (≥20% Improvement) for FASB Patients with EF ≥25 and NYHA=3 at Baseline

Population	Control n/N (%)	Optimizer n/N (%)	P-value[1]
FASB1	6/93 (6.45)	23/104 (22.12)	**0.0015**
FASB2	11/93 (11.83)	22/104 (21.15)	0.0587
FASB3	9/93 (9.68)	22/104 (21.15)	**0.0210**
FASB4	8/93 (8.60)	23/104 (22.12)	**0.0073**
FASB5	9/93 (9.68)	24/104 (23.08)	**0.0093**
FASB6	8/93 (8.60)	21/104 (20.19)	**0.0172**
FASB7	11/93 (11.83)	22/104 (21.15)	0.0587
FASB8	8/93 (8.60)	22/104 (21.15)	**0.0113**
FASB9	8/93 (8.60)	24/104 (23.08)	**0.0047**
FASB10	11/93 (11.83)	23/104 (22.12)	0.0419

[1]One-sided Fisher's exact test

The analysis of the combined imputations for FASB (EF≥25 and NYHA=3) resulted in a z=-2.1549 with corresponding P=0.0156.

Theses imputation analyses by ITT, FASA, or FASB all resulted in similar outcomes. The whole population does not demonstrate statistical significance at a 0.025. The sub group of patients with baseline EF≥25 results in a P-value less than 0.05, but slightly above the 0.025 value and the sub-group with EF≥25 and NYHA=3 achieves statistical significance with P<0.025.

XIII. Secondary Effectiveness Analyses

The mean AT and PVO2 at Baseline, 24 weeks and 50 weeks for the CC population are given in the table below.

Table XIII.1a Mean AT and PVO2 at Study Time Points

Variable	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
AT	Baseline	10.97 (2.18) 207 10.73 (5.40, 17.05)	10.95 (2.24) 201 10.60 (5.29, 16.92)	0.9528[1]
	24 Week	10.96 (2.20) 158 10.83 (6.24, 19.61)	10.87 (2.45) 169 10.49 (5.01, 19.82)	0.7346[1]
	24 Week Difference From Baseline	-0.14 (2.14) 154 -0.23 (-4.99, 9.34)	-0.14 (2.23) 159 -0.25 (-6.47, 8.94)	0.5040[3]
	50 Week	10.92 (2.49) 148 10.78 (4.10, 20.93)	11.10 (2.56) 163 10.92 (5.40, 21.83)	0.5471[1]
	50 Week Difference From Baseline	-0.14 (2.64) 146 -0.35 (-6.45, 10.66)	0.01 (2.59) 156 -0.30 (-5.43, 12.25)	0.3158[3]
PVO2	Baseline	14.71 (2.92) 211 15.02 (8.54, 22.61)	14.73 (3.06) 214 14.48 (8.43, 23.02)	0.9245[1]
	24 Week	14.54 (3.56) 169 14.47 (6.30, 27.95)	14.94 (3.62) 179 14.47 (7.63, 27.49)	0.3008[1]
	24 Week Difference From Baseline	-0.41 (2.90) 168 -0.50 (-7.68, 11.60)	0.24 (3.16) 179 -0.04 (-8.17, 11.69)	0.0242[3]
	50 Week	14.59 (3.87) 159 14.47 (6.88, 29.75)	14.72 (3.51) 172 14.47 (8.12, 30.67)	0.7394[1]
	50 Week Difference From Baseline	-0.44 (3.01) 152 -0.58 (-7.80, 12.06)	-0.08 (3.47) 164 -0.21 (-6.87, 17.45)	0.2330[3]

[1]Two-sided equal variance Student's t-test.
[2]Two-sided unequal variance Student's t-test
[3]One-sided equal variance Student's t-test

The responder analyses for the CC population at 24 and 50 weeks are provided in the table below.

Table XIII.1b Responder Analysis (20% or Greater improvement from Baseline) at Study Time Points

Variable	Time	Control n/N (%)	Optimizer n/N (%)	P-value[1]
AT	24 Week	18/154 (11.69)	28/159 (17.61)	0.0932
	50 Week	21/146 (14.38)	37/156 (23.72)	0.0275
PVO2	24 Week	23/168 (13.69)	31/179 (17.32)	0.2169
	50 Week	24/158 (15.19)	31/172 (18.02)	0.2944

[1]One-sided Fisher's exact test

Note that the responder analysis for 24 weeks has a P-value of less than 0.1 and for 50 weeks has a P-value that is near 0.025.

XIV. Additional Analyses

Analyses of additional endpoints are presented below. The means for the quality of life instrument, the MLWHFQ, the NYHA, and the 6 minute walk test (MWT) are provided at 24 and 50 weeks below.

Table XIV.1a Mean AT and PVO2 at Study Time Points

Variable	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
MLWHFQ	Baseline	57.38 (22.62) 213 59.0 (1.0, 102.0)	60.49 (23.00) 215 64.0 (0.0, 100.0)	0.1595[1]
	24 Week	52.08 (23.84) 184 53.5 (0.0, 105.0)	45.33 (24.43) 196 46.0 (0.0, 97.0)	0.0068[1]
	24 Week Difference From Baseline	-5.72 (21.03) 184 -6.0 (-74.0, 68.0)	-15.38 (19.55) 196 -12.5 (-81.0, 25.0)	**<0.0001**[3]
	50 Week	51.10 (23.57) 173 53.0 (1.0, 101.0)	42.75 (25.66) 183 42.0 (0.0, 101.0)	**0.0015**[1]
	50 Week Difference From Baseline	-7.32 (20.66) 173 -6.0 (-81.0, 87.0)	-17.60 (22.68) 183 -15.0 (-81.0, 43.0)	**<0.0001**[3]
NYHA	Baseline	3.13 (0.35) 213 3.0 (2.0, 4.0)	3.09 (0.28) 215 3.0 (3.0, 4.0)	0.1650[2]
	24 Week	2.81 (0.71) 183 3.0 (1.0, 4.0)	2.53 (0.73) 191 3.0 (1.0, 4.0)	**0.0002**[2]
	24 Week Difference From Baseline	-0.32 (0.73) 183 0.0 (-2.0, 1.0)	-0.54 (0.72) 191 0.0 (-3.0, 1.0)	**0.0015**[3]
	50 Week	2.67 (0.78) 174 3.0 (1.0, 4.0)	2.48 (0.85) 185 3.0 (1.0, 4.0)	**0.0232**[2]
	50 Week Difference From Baseline	-0.47 (0.83) 173 0.0 (-3.0, 1.0)	-0.61 (0.86) 185 -1.0 (-3.0, 1.0)	0.0598[3]
6 MWT	Baseline	323.99 (92.44) 212 321.0 (80.0, 600.0)	326.38 (82.10) 215 330.0 (95.0, 525.0)	0.7771[1]
	24 Week	335.13 (106.99) 173 340.0 (75.0, 730.0)	347.68 (95.47) 190 349.0 (90.0, 585.0)	0.2384[1]
	24 Week Difference From Baseline	8.61 (85.08) 173 7.0 (-375.0, 457.0)	19.41 (80.62) 190 15.0 (-316.0, 301.0)	0.1079[3]
	50 Week	337.31 (109.49) 162 342.0 (80.0, 823.0)	348.97 (98.34) 181 357.0 (55.0, 615.0)	0.2996[1]
	50 Week Difference From Baseline	10.51 (87.16) 162 14.0 (-375.0, 365.0)	20.22 (83.14) 181 13.0 (-220.0, 285.0)	0.1449[3]

[1]Two-sided equal variance Student's t-test.
[2]Two-sided unequal variance Student's t-test
[3]One-sided equal variance Student's t-test

A responder analysis with response being defined as -10 or more points for the MLWHFQ, -1 or more classes for the NYHA, and 40 meters or more for the 6 MWT.

Table XIV.1b Responder Analysis at Study Time Points

Variable	Time	Control n/N (%)	Optimizer n/N (%)	P-value[1]
MLWHFQ[2]	24 Week	77/184 (41.85)	110/196 (56.12)	**0.0037**
	50 Week	73/173 (42.20)	112/183 (61.20)	**0.0002**
NYHA[3]	24 Week	63/183 (34.43)	94/191 (49.21)	**0.0026**
	50 Week	80/174 (45.98)	97/185 (52.43)	0.1320
6 MWT[4]	24 Week	51/173 (29.48)	65/190 (34.21)	0.1970
	50 Week	51/162 (31.48)	69/181 (38.12)	0.1201

[1]One-sided Fisher's Exact Test
[2]Responder is a 10 or more point improvement from baseline.
[3]Responder is a 1 or more point improvement from baseline.
[4]Responder is a 40 or more meters improvement from baseline.

Note that there are higher proportions of responders in the Optimizer group for all of the endpoints and time periods. The P-value for patients experiencing a 10 or more point decline in the MLWHFQ at both 24 and 50 weeks are highly statistically significant and NYHA at 24 weeks.

The means for the 24 and 50 week changes in AT and PVO2 are presented for the sub-group with EF≥25 for the CC population in the table below.

Table XIV.2a Mean AT and PVO2 at Study Time Points in Sub-group with Baseline EF≥25

Variable	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
AT	Baseline	11.17 (2.30) 112 10.74 (5.40, 17.05)	10.68 (2.12) 110 10.39 (5.29, 16.08)	0.1035[1]
	24 Week	10.89 (2.11) 80 10.80 (6.24, 15.50)	11.00 (2.45) 94 10.46 (5.01, 19.82)	0.7542[1]
	24 Week Difference From Baseline	-0.44 (1.93) 79 -0.38 (-3.79, 5.64)	0.04 (2.32) 88 -0.15 (-4.65, 8.94)	0.0745[2]
	50 Week	11.00 (2.31) 77 10.97 (4.10, 17.54)	11.11 (2.36) 95 11.16 (5.40, 20.62)	0.7525[1]
	50 Week Difference From Baseline	-0.27 (2.38) 77 -0.39 (-5.32, 6.62)	0.23 (2.41) 91 0.09 (-5.05, 8.31)	0.0878[2]
PVO2	Baseline	14.95 (2.83) 112 15.09 (8.68, 22.61)	14.59 (2.95) 117 14.48 (8.43, 20.96)	0.3539[1]
	24 Week	14.21 (3.02) 89 14.10 (6.30, 20.37)	14.99 (3.48) 99 14.84 (7.63, 27.49)	0.1020[1]
	24 Week Difference From Baseline	-1.00 (2.47) 89 -0.96 (-6.54, 6.01)	0.32 (3.04) 99 -0.03 (-6.58, 11.69)	**0.0006**[3]
	50 Week	14.63 (3.46) 81 14.43 (6.88, 24.51)	14.73 (3.23) 100 14.75 (8.12, 27.19)	0.8446[1]
	50 Week Difference From Baseline	-0.68 (2.93) 81 -0.55 (-6.40, 7.05)	0.08 (3.00) 100 -0.00 (-6.36, 11.38)	0.0436[2]

[1]Two-sided equal variance Student's t-test.
[2]One-sided equal variance Student's t-test
[3]One-sided unequal variance Student's t-test

The responder analysis for this sub-group in the CC population is presented in the following table.

Table XIV.2b. Responder Analysis (20% or Greater improvement from Baseline) at Study Time Points in Sub-group with Baseline EF≥25

Variable	Time	Control n/N (%)	Optimizer n/N (%)	P-value[1]
AT	24 Week	6/79 (7.59)	17/88 (19.32)	**0.0230**
	50 Week	10/77 (12.99)	24/91 (23.53)	**0.0240**
PVO2	24 Week	4/89 (4.49)	18/99 (18.18)	**0.0028**
	50 Week	10/81 (12.35)	19/100 (19.00)	0.1563

[1]One-sided Fisher's Exact Test

For this sub-group of CC patients, both at 24 and 50 weeks the AT responders were significantly greater in Optimizer patients both with P-values below 0.025.

The means for the other variables for the CC sub-group with EF≥25 are presented below.

Table XIV.3a Mean AT and PVO2 at Study Time Points in Sub-group with Baseline EF≥25

Variable	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value[1]
MLWHFQ	Baseline	56.57 (23.59) 113 59.0 (1.0, 102.0)	59.73 (23.23) 117 64.0 (4.0, 99.0)	0.3072[1]
	24 Week	52.38 (24.29) 97 54.0 (0.0, 101.0)	43.93 (24.41) 108 44.5 (0.0, 97.0)	**0.0139**[1]
	24 Week Difference From Baseline	-5.52 (21.68) 97 -5.0 (-74.0, 68.0)	-16.34 (20.19) 108 -17.0 (-67.0, 24.0)	**0.0001**[3]
	50 Week	53.71 (23.60) 90 55.0 (1.0, 101.0)	42.98 (25.75) 103 41.0 (0.0, 101.0)	**0.0030**[1]
	50 Week Difference From Baseline	-4.50 (21.23) 90 -6.0 (-66.0, 87.0)	-17.65 (22.61) 103 -17.0 (-78.0, 43.0)	**<0.0001**[3]
NYHA	Baseline	3.12 (0.36) 113 3.0 (2.0, 4.0)	3.07 (0.25) 117 3.0 (3.0, 4.0)	0.1766[2]
	24 Week	2.88 (0.65) 94 3.0 (1.0, 4.0)	2.54 (0.65) 103 3.0 (1.0, 4.0)	**0.0003**[1]
	24 Week Difference From Baseline	-0.24 (0.67) 94 0.0 (-2.0, 1.0)	-0.51 (0.68) 103 0.0 (-3.0, 1.0)	**0.0028**[3]
	50 Week	2.73 (0.79) 91 3.0 (1.0, 4.0)	2.41 (0.81) 106 2.5 (1.0, 4.0)	**0.0059**[1]
	50 Week Difference From Baseline	-0.43 (0.83) 91 0.0 (-3.0, 1.0)	-0.66 (0.83) 106 -1.0 (-3.0, 1.0)	**0.0257**[3]
6 MWT	Baseline	326.83 (94.49) 112 330.0 (120.0, 600.0)	325.80 (84.24) 117 321.0 (95.0, 525.0)	0.9308[1]
	24 Week	333.73 (97.67) 91 340.0 (89.0, 644.0)	344.91 (99.17) 104 346.0 (90.0, 585.0)	0.4296[1]
	24 Week Difference From Baseline	3.88 (80.19) 91 4.0 (-375.0, 255.0)	18.75 (82.49) 104 15.5 (-316.0, 225.0)	0.1028[3]
	50 Week	334.64 (103.60) 83 352.0 (85.0, 514.0)	345.51 (100.48) 103 358.0 (55.0, 615.0)	0.4701[1]
	50 Week Difference From Baseline	2.89 (90.81) 83 15.0 (-375.0, 225.0)	20.29 (87.37) 103 19.0 (-210.0, 285.0)	0.0926[3]

[1]Two-sided equal variance Student's t-test.
[2]Two-sided unequal variance Student's t-test
[3]One-sided equal variance Student's t-test

For the responders in this sub-group of the CC population the following table gives the results.

Table XIV.3b Responder Analysis at Study Time Points in Sub-group with Baseline EF≥25

Variable	Time	Control n/N (%)	Optimizer n/N (%)	P-value[1]
MLWHFQ[2]	24 Week	40/97 (41.24)	63/108 (58.33)	**0.0105**
	50 Week	34/90 (37.78)	64/103 (62.14)	**0.0006**
NYHA[3]	24 Week	27/94 (28.72)	47/103 (45.63)	**0.0105**
	50 Week	42/91 (46.15)	57/106 (53.77)	0.1779
6 MWT[4]	24 Week	24/91 (26.37)	38/104 (36.54)	0.0856
	50 Week	27/83 (32.53)	37/103 (35.92)	0.3718

[1]One-sided Fisher's Exact Test
[2]Responder is a 10 or more point improvement from baseline.
[3]Responder is a 1 or more point improvement from baseline.
[4]Responder is a 40 or more meters improvement from baseline.

These results show that MLWFHQ (at 24 and 50 weeks) and NYHA (at 24 weeks) demonstrate statistically significant results with P<0.025.

The means AT and PVO2 for the CC sub-group with EF≥25 and NYHA =3 appear in the table below.

Table XIV.4a Mean AT and PVO2 at Study Time Points in Sub-group with Baseline EF≥25 and NYHA = 3

Variable	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
AT	Baseline	11.22 (2.18) 96 10.74 (7.22, 16.72)	10.63 (2.09) 103 10.38 (5.29, 16.05)	0.0521[1]
	24 Week	10.87 (2.15) 70 10.67 (6.24, 15.50)	11.03 (2.49) 88 10.53 (5.01, 19.82)	0.6750[1]
	24 Week Difference From Baseline	-0.54 (1.83) 69 -0.49 (-3.79, 4.62)	0.10 (2.36) 83 -0.11 (-4.65, 8.94)	0.0310[3]
	50 Week	10.91 (2.25) 66 10.95 (4.10, 17.54)	11.18 (2.40) 90 11.21 (5.40, 20.62)	0.4736[1]
	50 Week Difference From Baseline	-0.44 (2.27) 66 -0.48 (-5.32, 4.81)	0.28 (2.43) 86 0.12 (-5.05, 8.31)	0.0317[3]
PVO2	Baseline	15.06 (2.72) 96 15.09 (9.30, 22.61)	14.56 (2.91) 109 14.48 (8.43, 20.88)	0.2074[1]
	24 Week	14.44 (2.96) 76 14.39 (8.61, 20.37)	14.94 (3.49) 94 14.67 (7.63, 27.49)	0.3188[1]
	24 Week Difference From Baseline	-0.97 (2.31) 76 -0.81 (-6.35, 4.16)	0.34 (3.11) 94 0.01 (-6.58, 11.69)	**0.0010[3]**
	50 Week	14.65 (3.42) 69 14.43 (6.88, 24.51)	14.82 (3.27) 93 14.93 (8.12, 27.19)	0.7425[1]
	50 Week Difference From Baseline	-0.79 (2.79) 69 -0.73 (-6.40, 7.05)	0.20 (3.04) 93 0.07 (-6.36, 11.38)	**0.0174[3]**

[1]Two-sided equal variance Student's t-test.
[2]One-sided equal variance Student's t-test
[3]One-sided equal variance Student's t-test

The responder analysis for this sub-group appears in the table below.

Table XIV.4b Responder Analysis (20% or Greater improvement from Baseline) at Study Time Points in Sub-group with EF≥25 and NYHA = 3

Variable	Time	Control n/N (%)	Optimizer n/N (%)	P-value[1]
AT	24 Week	4/69 (5.80)	17/83 (20.48)	**0.0073**
	50 Week	8/66 (12.12)	23/86 (26.74)	**0.0205**
PVO2	24 Week	3/76 (3.95)	18/94 (19.15)	**0.0020**
	50 Week	8/69 (11.59)	19/93 (20.43)	0.0993

[1]One-sided Fisher's Exact Test

The responders in AT for both 24 and 50 weeks demonstrate an advantage for Optimizer patients with P-values less than 0.025 and the responders with PVO2 demonstrate an advantage for Optimizer patients at 24 weeks with a P<0.025.

The means for the remaining effectiveness variables for the sub-group of CC patients with EF≥25 and NYHA = 3 are in the table below.

Table XIV.5a Mean AT and PVO2 at Study Time Points in Sub-group with EF≥25 and NYHA = 3

Variable	Time	Control Mean (SD) N Med (Min, Max)	Optimizer Mean (SD) N Med (Min, Max)	P-value
MLWHFQ	Baseline	53.92 (23.59) 97 58.0 (1.0, 93.0)	59.80 (22.97) 109 64.0 (4.0, 99.0)	0.0716[1]
	24 Week	49.20 (23.60) 84 51.0 (0.0, 95.0)	43.89 (23.63) 101 44.0 (0.0, 97.0)	0.1295[1]
	24 Week Difference From Baseline	-5.98 (21.85) 84 -4.5 (-74.0, 68.0)	-16.76 (20.23) 101 -18.0 (-67.0, 24.0)	**0.0003**[2]
	50 Week	51.63 (22.70) 76 54.5 (1.0, 93.0)	42.05 (25.45) 97 40.0 (0.0, 101.0)	**0.0109**[1]
	50 Week Difference From Baseline	-3.68 (19.07) 76 -5.5 (-62.0, 87.0)	-18.25 (22.26) 97 -18.0 (-78.0, 32.0)	**<0.0001**[3]
NYHA	Baseline	3.0 (0.0) 97 3.0 (3.0, 3.0)	3.0 (0.0) 109 3.0 (3.0, 3.0)	--
	24 Week	2.83 (0.64) 82 3.0 (1.0, 4.0)	2.54 (0.61) 97 3.0 (1.0, 4.0)	**0.0022**[1]
	24 Week Difference From Baseline	-0.17 (0.64) 82 0.0 (-2.0, 1.0)	-0.46 (0.61) 97 0.0 (-2.0, 1.0)	**0.0011**[2]
	50 Week	2.69 (0.77) 77 3.0 (1.0, 4.0)	2.38 (0.80) 99 2.0 (1.0, 4.0)	**0.0118**[1]
	50 Week Difference From Baseline	-0.31 (0.77) 77 0.0 (-2.0, 1.0)	-0.62 (0.80) 99 -1.0 (-2.0, 1.0)	**0.0060**[3]
6 MWT	Baseline	333.59 (87.82) 96 340.0 (122.0, 600.0)	330.61 (79.14) 109 330.0 (134.0, 525.0)	0.7986[2]
	24 Week	341.19 (98.81) 79 346.0 (89.0, 644.0)	352.93 (96.00) 97 360.0 (100.0, 585.0)	0.4270[1]
	24 Week Difference From Baseline	0.84 (82.58) 79 0.0 (-375.0, 255.0)	21.54 (77.54) 97 16.0 (-305.0, 225.0)	0.0445[3]
	50 Week	342.44 (101.77) 70 356.0 (85.0, 514.0)	351.15 (95.41) 95 358.0 (105.0, 615.0)	0.5742[1]
	50 Week Difference From Baseline	0.91 (96.20) 70 12.0 (-375.0, 225.0)	20.45 (87.28) 95 20.0 (-210.0, 285.0)	0.0879[3]

[1]Two-sided equal variance Student's t-test.
[2]One-sided unequal variance Student's t-test
[3]One-sided equal variance Student's t-test

The responder analysis corresponding to the table above appears in the table below.

Table XIV.5b Responder Analysis at Study Time Points in Sub-group with EF≥25 and NYHA = 3

Variable	Time	Control n/N (%)	Optimizer n/N (%)	P-value[1]
MLWHFQ[2]	24 Week	35/84 (41.67)	60/101 (59.41)	**0.0119**
	50 Week	28/76 (36.84)	61/97 (62.89)	**0.0006**
NYHA[3]	24 Week	19/82 (23.17)	43/97 (44.33)	**0.0023**
	50 Week	32/77 (41.56)	51/99 (51.52)	0.1229
6 MWT[4]	24 Week	20/79 (25.32)	36/97 (37.11)	0.0652
	50 Week	22/70 (31.43)	35/95 (36.84)	0.2895

[1]One-sided Fisher's Exact Test
[2]Responder is a 10 or more point improvement from baseline.
[3]Responder is a 1 or more point improvement from baseline.
[4]Responder is a 40 or more meters improvement from baseline.

These analyses indicate that for CC patients with EF≥25 and NYHA = 3, Optimizer patients have greater response than control patients and it is significantly greater for MLWHFQ and NYHA at 24 weeks and for MLWHFQ at 50 weeks with a P<0.025.

These additional analyses indicate that Optimizer patients had greater changes from baseline than control patients across all measures. Statistical significance in responder analyses with P-values less than 0.025 was achieved for all Optimizer CC patients for MLWHFQ overall at 24 and 50 weeks and NYHA for 24 weeks. For patient sub-grouped with EF≥25 whether or not the NYHA =3, the AT responder analysis demonstrated superiority for the Optimizer patients with P-values less than 0.025 at both 24 and 50 weeks. In these patients, the PVO2 demonstrated a significant advantage for Optimizer patients at 24 weeks.

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