Evaluation of the Safety and Efficacy of the OPTIMIZER® System in Subjects with Moderate-to-Severe Heart Failure with Ejection Fraction between 25% and 45%: FIX-HF-5C

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I. TITLE

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II. BACKGROUND INFORMATION

A. Name and description of investigational product

The investigational product is the OPTIMIZER IVs 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 four major components:

1. An implantable **pulse generator** with specialized internal components that generate the cardiac contractility modulation (CCM) signal (the OPTIMIZER IVs 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.

   NOTE: For purposes of this study, any commercially available atrial lead can be used. For the ventricular sensing and CCM delivery leads, the following leads may be used:

   - Biotronik Setrox S45, S53 and S60 lead
   - Boston Scientific Dextrus 4135, 4136 and 4137 lead
   - St. Jude Tendril DX 1688T, 1788T, 1888 or 2088 active fixation lead
   - 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 (OMNI II Programmer);
4. A **battery charging system**, consisting of a charger unit and wand (Mini Charger);

The OPTIMIZER IVs is very similar in its design, and is substantially equivalent, to the OPTIMIZER III System with regard to its intended use, safety, performance, and design characteristics. The design of the OPTIMIZER IVs includes several differences intended to offer physicians and patients a smaller IPG, a portable charger and an easier to use programmer. Despite these differences the critical aspects of the device design (the device algorithms, sensing signals, CCM signal outputs and functionality) all remain identical.

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/dtmax, dP/dtmin, 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.

(5) Prospective, multicenter, randomized double blind study of CCM: the FIX-CHF-4 study (Europe)

A multicenter, randomized, double-blinded study (FIX-CHF-4) was conducted to evaluate the safety and effectiveness of the OPTIMIZER II and OPTIMIZER III systems in subjects with New York Heart Association (NYHA) class II and III heart failure. A total of 164 subjects with ischemic (60%) or idiopathic (40%) cardiomyopathy, EF<35%, NYHA Class II (24%) or III (76%) received a CCM pulse generator. Patients were randomly assigned to Group 1 (n=80, CCM treatment 3 months, sham treatment second 3 months) or Group 2 (n=84, sham treatment 3 months, CCM treatment second 3 months). The co-primary endpoints were differences between groups of changes in peak oxygen consumption ($VO_{2\ peak}$) and Minnesota Living with Heart Failure Questionnaire (MLWHFQ). 164 subjects with ejection fraction <35% and NYHA Class II (24%) or III (76%) symptoms received a CCM pulse generator. Baseline EF (29.3±0.9% vs. 29.8±1.12%), peak oxygen consumption ($VO_{2,peak}$, 14.1±0.3 vs. 13.6±0.3 ml/kg/min) and Minnesota Living with Heart Failure Questionnaire (MLWHFQ, 38.4±2.1 vs. 36.5±2.11) were similar in both groups. For VO2,peak and MLWHFQ, a statistically significant benefit was noted during periods of active treatment compared to sham treatment. The mean improvement in patients' $VO_{2,peak}$ during the periods of active treatment was 1.03 ± 2.78 (p=0.03 via t-test) with 95% confidence interval of (0.09, 1.98). For MLWHFQ, mean improvement during patients' active treatment was 5.85 ± 16.03 (p=0.03 via t-test) with 95% confidence interval of (0.59, 11.11).

There were 6 deaths during the study, two prior to randomization (ventricular fibrillation and worsening heart failure), one in Group 1 during the OFF period (undetermined cause), one in Group 2 during the OFF period and two in Group 2 during the ON period (sudden cardiac death and renal failure).

In total, there were 48 serious adverse events in 40 patients during CCM OFF periods, compared to 45 serious adverse events in 41 patients during CCM

ON periods. The most frequently reported events were episodes of decompensated heart failure, atrial fibrillation, bleeding at the OPTIMIZER System implant site and pneumonia. There were no significant differences between ON and OFF phases in the number or types of adverse events. Adverse events specifically related to the device and/or the procedure as reported by the investigators included lead dislodgement, device pocket infections, bleeding at the insertion site and pericardial effusion. Investigators listed several other events as being of "unknown" relationship to the device and/or procedure, including atrial fibrillation, episodes of heart failure exacerbations, cardiogenic shock, angina, ventricular tachycardia and ICD sensing defect.

Because of the crossover design, hospitalizations and mortality were analyzed for the first period only. In all there were 14 hospitalizations Group 1 patients (CCM ON phase) compared to 20 hospitalizations in Group 2 patients (CCM OFF phase). In addition there was 1 death in a Group 2 patient versus no deaths in Group 1 patients. With the relatively small sample size the overall event-free survival did not reach statistical significance ($p=0.31$).

Another safety endpoint in the study was an evaluation of whether the use of the OPTIMIZER Systems was associated with changes in the incidence and nature of arrhythmias assessed by Holter monitoring. At baseline, the total number of PVCs/hour was balanced between groups with median (range) values of 21 (0-511) and 25 (0-712) in Groups 1 and 2, respectively. During ON periods, there was a median of 20 (0-777) and 17 (0-459) PVCs/hour in Groups 1 and 2, respectively, compared to 16 (0-1007) and 15 (0-764) during the OFF periods. In addition, there were no significant differences in other Holter parameters between baseline and follow up in either group.

Overall, the results of this study suggested that the device improves quality of life and exercise tolerance and appears safe when used over 3 months time.

(6) US Feasibility IDE Trial: The FIX HF-5, Phase I Study (US)

On May 6, 2004, the FDA granted conditional approval for human trials to begin in the United States. The US Feasibility Study (also referred to as the Phase I Study) was designed to evaluate the safety and effectiveness of the OPTIMIZER II System with active fixation leads in subjects with moderate and severe heart failure. The investigation was designed as a multi-center, randomized, double-blind study at 10 sites nationwide. This was a randomized, double blind pilot study of the safety and efficacy of CCM in heart failure patients with normal QRS duration. Methods: 49 subjects with medically refractory NYHA Class III symptoms were successfully implanted with a CCM pulse generator and two leads inserted into the RV septum. Forty-nine (49) subjects were randomized to have their devices programmed to deliver CCM signals (Treatment, n=25) or to remain off (Control, n=24) for 6 months. Evaluations (double blind) included 6-minute hall walk, echocardiography, cardiopulmonary stress test and Minnesota Living with Heart Failure Questionnaire (MLWHFQ). Results: Although most baseline features were balanced between groups, ejection fraction (31.4±7.4 vs. 24.9±6.5%, p=0.003) and peak VO_2 (16.0±2.9 vs. 14.3±2.8 ml O_2/kg/min, p=0.02) were lower in the Treatment group versus the Control. Nevertheless, freedom from hospitalization at 6 months was 65 vs. 80% in Control vs. Treatment. Freedom from death was 100% in both groups at 6-months. Compared to baseline, 6MW increased 13.4 meters, peak VO_2 increased 0.2 ml O_2/kg/min and anaerobic threshold increased 0.8 ml O_2/kg/min more in the Treatment group than the Control group. With the small number of subjects none of the differences were statistically significant. Conclusions: Even though the Treatment group was sicker at baseline, event-free survival, adverse event profiles and measures of effectiveness trended to be better in the treatment group. These results warrant large scale studies of safety and effectiveness of CCM.

(7) US Pivotal IDE Trial: The FIX HF-5 Phase II Study (US)

The US Pivotal Trial (also referred to as the Phase II Study) was conducted under an IDE granted by the FDA (G030099/S7). This study tested safety and efficacy of CCM in 428 NYHA III or IV heart failure patients on optimal medical treatment (OMT) with EF≤35% (as quantified by site echocardiographers) and narrow QRS randomized to CCM plus OMT (n=215) or OMT alone (n=213). Efficacy was assessed by anaerobic threshold (AT, primary endpoint), peak VO_2 (pVO_2) and Quality of Life (QoL) score at 6 months; total follow up was 12 months. The primary safety endpoint was a test of noninferiority between groups at 12 months of the composite of all-cause mortality and all cause hospitalizations (12.5% allowable delta). The groups were matched for age (56±14 vs 59±12 yrs), EF (27±6 vs 26±7%), pVO_2 (14.6±3.3 vs 14.8±3.0 ml/kg/min) and all other characteristics. While AT did not improve at 6 months, pVO_2 and QoL were improved by CCM (by 0.65 ml/kg/min, p=0.024 and -9.7 points, p<0.0001, respectively) over OMT. 48% of OMT and 52%of CCM patients experienced a safety endpoint, which satisfied the non-inferiority criteria (p=0.03). In patients with EF≥25% (as determined by the echo core lab) and NYHA III (n=185), AT (0.64 ml/kg/min, p=0.03), pVO_2 (1.31 ml/kg/min, p=0.001) and QoL (10.8 points, p=0.003) improved more in the CCM group. Findings were similar at 12 months and results of responders analyses applied to all variables were also significant (p<0.01) in this group. Furthermore, when peak VO_2 was analyzed as a continuous variable, it was observed that for patients with EF≥25% the treatment group experienced a statistically and clinically significant improvement over controls through 12 months, regardless of NYHA class (further details provided below in Statistical Analysis section). Thus, the study showed that when used in patients with narrow QRS and NYHA Class III or IV symptoms on OMT, CCM is safe and improves pVO_2 and QoL at 6 months. In the prespecified subgroup analysis, CCM appeared more effective in patients with EF≥25% as evidence by significant improvements in pVO_2 at 6 months, findings that were sustained through 12 months.

Furthermore, subjects were deemed eligible and enrolled based on the site assessment of EF, but since each study was also assessed in an echocardiographic core lab, it turned out that 38 of the study subjects (20 in OMT and 18 OMT+CCM) had EFs greater than 35% per core lab assessment. For this subgroup, the EF average was 38±3% (range 35-45%) and did not differ between groups. At the 6 month endpoint, peak VO_2 increased by 1.66+0.42 ml/kg/min in OMT+CCM versus a 1.30+0.73 ml/kg/min *decrease* in OMT, a difference of 2.96 mlO2/kg/min (p=0.03). MLWHFQ decreased by 19±22 points in OMT+CCM versus 1±29 point in OMT, a mean difference of 18 points (p=0.06). 6MW increased by 43±80 meters in OMT+CCM versus a *decrease* of 10±97meters in OMT, a mean difference of 53 meters (p=0.11). The results of this additional hypothesis generating subgroup analysis indicate that CCM has the potential to provide clinically significant benefits in patients with medically refractory CHF with EF between 35 and 45%.

In aggregate, the results of prior studies suggest that the OPTIMIZER System functions as intended and preliminary evidence suggests that CCM therapy could provide clinical benefit especially in a subset of subjects with ejection fraction ≥25%.

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. Invasive aspects and the associated risks of the OPTIMIZER implant procedure and device system are described below. Additionally, there may be an increased risk of death associated with the application of cardiac contractility modulation therapy. Applying appropriate subject selection criteria, using meticulous techniques and providing attentive post-procedure care will minimize the risks associated with these procedures.

b. 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.

c. 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.

d. 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.

e. 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.

f. Thromboembolic Events

Thrombosis or embolism may occur as a result of the placement of the leads for the OPTIMIZER System or as a result of the underlying disease. These events may include deep vein thrombosis, renal vein thrombosis, pulmonary embolism, transient ischemic attacks (TIA), stroke, 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.

g. 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.

h. 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.

i. 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.

j. Vascular laceration and bleeding

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

k. 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.

l. 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.

m. 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.

n. 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).

o. 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 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 (7.5V) 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 and Phase II of the FIX-HF-5 studies utilized an intermediate dose of 5 hour/day signal delivery paradigm. Since the safety profile during Phase I and Phase II 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 other region-specific 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 most likely to benefit from application of CCM signals. The population is generally characterized by NYHA Class III and IV symptoms, an ejection fraction between 25 and 45% (inclusive) and peak VO_2 between 9 and 20 ml O2/kg/min.

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 medically refractory moderate-to-severe heart failure characterized by an ejection fraction between 25% and 45% and peak VO_2 between 9 and 20 ml O_2/kg/min. 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 24 weeks following the date of scheduled implantation, shall consist of the following parameter:

Improvement in exercise tolerance quantified by peak VO_2 measured on cardiopulmonary exercise stress testing (CPX) and evaluated by a blinded core lab. The primary endpoint will be a comparison of mean changes from baseline to 24-weeks between control and treatment groups.

2. Secondary efficacy endpoints
   a. Improvement in quality of life, as assessed by the Minnesota Living with Heart Failure (MLWHF) Questionnaire.
   b. Comparison of mean changes in peak VO_2 between groups with change in respiratory exchange ratio (RER) included as a covariate in the analysis.
   c. Improvement in heart failure class, as assessed by the New York Heart Association (NYHA) classification. NYHA classification shall be assigned by a blinded on site clinician according to their standard clinical practice. The analysis of this endpoint will test that hypothesis that the subjects treated with the OPTIMIZER will have a greater proportion of subjects that improve by at least one NYHA category than the control group.
   d. Comparison of mean change in peak VO_2 between groups in an analysis that only includes tests with a peak RER of ≥ 1.05
3. Other efficacy endpoints
   a. Comparison of mean change in 6 minute hall walk test between baseline and 24 weeks
   b. Comparison of mean change in VE/VCO_2 between baseline and 24 weeks as measured on a cardiopulmonary stress test.
4. The primary safety endpoint of this trial shall be:
   The proportion of subjects experiencing an OPTIMIZER device- or procedure-related complication through the 24-week follow up period, as determined by an independent events committee (Section IV.E.). Satisfying the primary safety endpoint will require demonstrating that the complication-free proportion is significantly higher than 70% (using a one-sided significance level of 0.025).
5. Other 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 composite rate of all-cause mortality and all-cause hospitalizations
d. the composite rate of cardiovascular mortality and heart failure-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. 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.

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 230 subjects with symptomatic 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 subjects will be followed for 24 weeks (**Figure 1)**. Evaluation of subjects will be documented on electronic case report forms and will include the tests and procedures listed in **Table 1.** The details of the Schedule of Events are provided in **Section VI.A.**

Figure 1. Study Overview

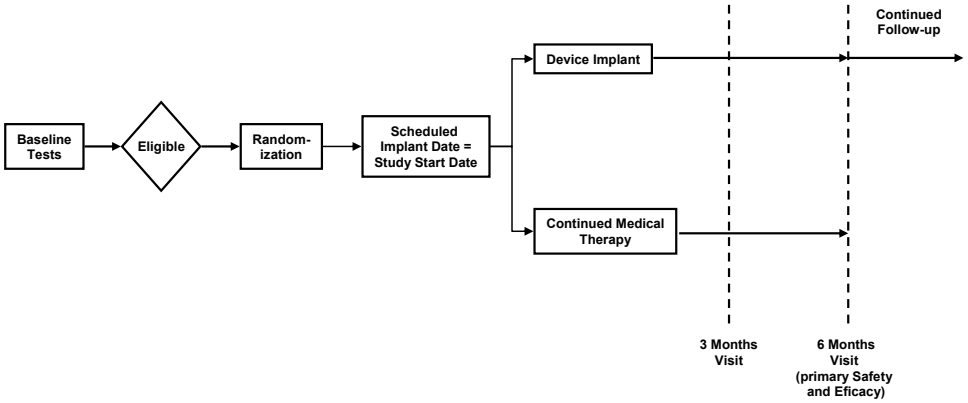

Table 1. Schedule of Events

Test or Assessment	Screening	Baseline	OPT Implant	Follow-Up Schedule (relative to Study Start Date§) Week 2 ±2 days§	+12±2 Weeks	+24±2 Weeks	Long-term F-up Every 6 Months** (relative to Study Start Date§) US Optimizer Group	US Control Group	EU OPT and Control
Informed Consent	X								
1-Year Medical History/Interim History	X			X	X	X	X		
NYHA Class (blinded site clinician assessment)	X				X	X			
Medications	X				X	X			
Physical Examination	X				X	X			
12-Lead EKG*		X							
24 hour Holter Monitor*		X							
Echocardiogram*		X							
MLWHFQ		X			X	X			
Cardiopulmonary Stress Test		2X			2X	2X			
6 Minute Walk Test		X				X			
Pregnancy test		X				X			
Eligibility determination		X							
Randomization		X							
OPTIMIZER System Implant			X						
Chest X-ray (prior to hospital discharge)			X						
OPTIMIZER Device Interrogation / Programming			X	X	X	X	X		
Adverse Events, Hospitalizations, and Procedures (as needed)/OPTIMZER device-related SAEs after 24-weeks		X	X	X	X	X	X		
Vital Status							X	X	X

§ Study Start Date (SSD): After completion and satisfying all entry criteria and prior to randomization, a date shall be scheduled for OPTIMIZER System implantation. This date shall serve as the start date for all subjects regardless of randomization assignment, from which all future follow-up visits are scheduled.

* 12-Lead EKG, 24-Hour Holter Monitor, and Echocardiogram test results (from the study-qualified lab) obtained within 30 days before informed consent and performed in accordance with the protocol, testing, and data collection requirements may be used for eligibility determination.

** US OPTIMIZER subjects are followed every 6 months (+/- 4 weeks) after the 24-week interval for device interrogation and reporting of OPTIMIZER Device related SAEs, if any. All other subjects are followed for vital status only, for 2 years following their SSD.

C. Anticipated Rate of Site and Patient Recruitment

Two hundred and thirty (230) study participants will be recruited from a maximum of 60 study sites over a period of approximately 2 years from study initiation. No site will be allowed to enroll more than 15% (35 subjects) into the study.

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 independent physicians and statisticians not otherwise affiliated with the study. 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 events. The classification shall include whether the event is related to either the OPTIMIZER device or to the OPTIMIZER procedure, and whether such an event constitutes a "complication" as defined by the Event Adjudication Committee. 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 subject 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 up to 60 clinical sites located in the United States and in Europe. A minimum of 115 subjects will be enrolled in the US; it is anticipated that approximately 30-50% of the subjects will be recruited from European sites.

3. Randomization

Subjects will be randomly assigned to one of two treatment groups with an allocation ratio of 1:1. 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.

4. Objective Primary Efficacy Endpoint

The primary efficacy endpoints of this study are chosen to provide as objective, reliable and practical as possible assessments of clinical and physiologic improvements. With regard to the physiologic assessment, peak VO_2 shall be used to assess efficacy. In order to minimize bias, , the subject will complete 2 tests at each time point and testers will be trained on how to ensure that subjects exercise to maximal effort. The blinded core laboratory will review the raw data of each and every test for quality and adequacy of testing requirements.

1. In order for a subject to be randomized, they must complete 2 baseline CPX tests. If the blinded core lab deems one of the two tests "inadequate", the data from the one "adequate" test shall be used for eligibility determination and final analysis.
2. Randomized subjects are required to complete two CPX tests at 12 weeks and two CPX tests at 24 weeks, also. If the subject refuses or is unable to complete one of the two tests, or if the core lab deems one of the two tests "inadequate", the data from the one "adequate" test shall be used for the final analysis. In cases where data from both tests are available, the values will be averaged and the resulting value will be used for data analysis.
3. Only tests deemed "adequate" by the blinded core lab will be used for study eligibility and study endpoint analyses.
4. The core lab can deem a test "inadequate" for any one of the following reasons:

a. the subject has an erratic or oscillatory breathing pattern

b. data is non-physiologic

c. testing equipment issues

d. the test is submaximal

4. Core Laboratories

A Core laboratory shall be used to analyze results of cardiopulmonary exercise tests and echocardiograms. All analyses shall be performed blinded to treatment assignment. Standard operating procedures (SOPs) for the core laboratory 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 24 weeks 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 (US requirement only), and that protects the device under normal conditions of shipping and handling. The leads will retain their commercial packaging and labeling.

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 7 months. This will include approximately one month for screening and baseline testing and a 24 week primary follow-up period. Following completion of the main portion of the study:

- Subjects with an OPTIMIZER device in the US shall continue to be followed clinically at 6 month intervals until the FDA has made a determination about the safety and efficacy of the device.
- All other subjects (US Control group and all non-US subjects) shall be followed for vital status only, every 6 months, until the 2 year vital status has been determined.

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 in the United States will be trained in the importance of accountability of investigational products. Impulse Dynamics engineers will install any OPTIMIZER System hardware required for the implant procedures and follow-up visits 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 complete the IDE Device Accountability Log for the IPG investigational components. Site clinical representatives will complete the IDE Device Accountability Log for all other investigational products including the OMNI II programmers, chargers, and Test Device Extension cables shipped to, used at, or returned from the clinical site.

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

Trial treatment randomization codes are pre-programmed into the Medidata EDC site. There are no procedures for breaking the codes as this is not a blinded clinical trial.

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 (eCRF). A listing of the case report forms is located in Appendix C. A separate source document should be available for each eCRF.

V. SELECTION AND WITHDRAWAL OF SUBJECTS

Two hundred and thirty (230) 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 greater than or equal to 25% and less than or equal to 45% by echocardiography determined by the echocardiography core laboratory.

NOTE: Echocardiograms performed within 30 days before patient informed consent may be used to determine study eligibility if the test was performed in accordance with the Echo Study SOP at the study-qualified echo laboratory.

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 subject is intolerant) and are in New York Heart Association functional Class III and 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 according to the region-specific guideline recommendations. For patients with EF≤35%, this regimen shall consist of the appropriate doses of diuretics, ACE-inhibitor or angiotensin II receptor blocker and β-blocker[1]. Ivabradine may also be considered in subjects with a heart rate ≥70bpm.[2] Stable is defined as no more than a 100% increase or 50% decrease in dose.

[1] The appropriate medical regimen for each subject will be determined by the care provider managing the patient. One or more of the "guideline-recommended" medications may not be appropriate for all patients (e.g. intolerance, allergy). In particular the use of diuretics is most often used for symptomatic relief, therefore in absence of symptoms, a diuretic may not be part of the optimal medical regimen. The use of ACE-I or ARB, beta-blocker, aldosterone antagonist, and diuretic should be considered in all subjects, however "appropriate" doses of these medications may be zero.

[2] Ivabradine should only be initiated after a stabilisation period of 4 weeks on optimised standard therapy with ACE inhibitors, beta-blockers and aldosterone antagonists.
http://www.servier.co.uk/pdfs/NICE_Guidance_20130617.pdf

d. Subjects who, in the opinion of the Principal Investigator (based on the current guidelines for clinical practice[3]), have a clinical indication for an implanted cardiac defibrillator (ICD, e.g., EF≤35%) 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.

NOTE: ICD implantations, when indicated in accordance with Investigator assessment, should be implanted prior to informed consent when reasonably possible. However, in the case where the indication for the device is only appreciated after informed consent, it must be implanted prior to study randomization. Use of the Core Lab LVEF evaluation is not required when determining ICD indication.

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

B. Subject exclusion criteria

1. Subjects whose baseline peak VO_2 is <9 or >20 ml O_2/min/kg.

   NOTE: Each CPX test deemed "adequate" by the Core Lab (one or both) must meet the eligibility criterion.

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

   NOTE: This exclusion relates to Mitral Valve Regurgitation as the cause of the heart failure. In the event that the physician decides to implant a MV Clip, the subject many not be evaluated for the protocol until a minimum of 90 days after the procedure.

3. Subjects who have clinically significant angina pectoris, consisting of angina during daily life (i.e., Canadian Cardiovascular Society Angina score of II or more), an episode of unstable angina within 30 days before enrollment, or angina

[3] 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

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 before 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.[4]

   NOTE: 24-Hour Holter monitoring performed within 30 days before patient informed consent may be used to determine study eligibility.

6. Subjects having a PR interval greater than 375 ms.

   NOTE: An ECG performed within one month before patient informed consent may be used to determine study eligibility.

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

   NOTE: Subjects cardioverted into normal sinus rhythm must be free of atrial tachyarrhythmias for a minimum of 30 days before patient informed consent.

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 perform baseline stress testing.

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, an accepted indication for such a device, or a QRS width of 130ms or greater.

    NOTE: An ECG performed within 30 days before patient informed consent may be used to determine study eligibility.

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[4] 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.
5. Holter readings less than 24 hours (eg., 20-24 hours) may be used to confirm protocol eligibility when the # of PVCs is such that extrapolation to 24 hours can reasonably predict a PVC burden less than 8,900 per 24 hours.

11. Subjects who have had a myocardial infarction within 90 days of enrollment.
12. Subjects who have mechanical tricuspid valve.
13. Subjects who have a prior heart transplant.
14. Subjects on dialysis.
15. Subjects who are participating in another experimental protocol.
16. 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 or Ethics Committee approved Informed Consent Form. All subjects who sign Informed Consent will be accounted for in the final report of this study. Subjects may be withdrawn from the study for the following reasons:

a. Voluntary decision to withdraw made by the subject. Options for a reduced level of participation will be discussed with randomized subjects prior to a decision to completely withdraw, if possible.
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 or circumstance 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 to ascertain their vital status for 2 years following their study start date. Every effort will be made to follow all subjects in both cohorts to assure as complete a data set as possible for the 24-week study period.

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 for the U. S. sites 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 US 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 patient privacy laws. For each subject, a medical history (inclusive of collecting 1-year pre-randomization history of hospitalizations), physical examination, demographic information and current usage of medications will be obtained.

2. Baseline Evaluation and Randomization

Baseline testing should not be initiated until the subject has been treated for heart failure for at least 90 days, and heart failure medications have been stable for a minimum of 30 days as outlined in section V.A.3.

All enrolled subjects will complete a Minnesota Living with Heart Failure Questionnaire and undergo an NYHA assessment, ECG, echocardiogram, 6 minute hall walk test (6MW), two cardiopulmonary stress tests (CPX, which shall include assessment of peak VO_2, peak RER and VE/VCO_2) and a 24-hour Holter monitor test (for assessment of the number PVCs).

<u>Baseline testing details:</u>

1. An echocardiogram performed within 30 days before informed consent may be used as the baseline test and protocol eligibility determination if the following criteria can be confirmed:
   - The echo was performed in accordance to the Echo SOP at a lab certified for the FIX-HF-5C Study, and
   - The patient was receiving optimal and stable heart failure medications as of the date the echo study was performed, and continues to be optimal and stable at the time of informed consent, and
2. A 24-hour Holter test performed within 30 days before informed consent may be used as the baseline test and protocol eligibility determination.
3. An ECG performed within 30 days before informed consent may be used as the baseline test and protocol eligibility determination.

4. The CPX test will be performed twice, with the second test being performed between 1 day (24 hours) and 7 days following the first test.
5. The 6MW and CPX tests may be performed on the same day, but must be performed a minimum of 3 hours apart, with the CPX test performed first.
6. Females of childbearing potential will undergo a pregnancy test within 7 days of the schedule implantation procedure.

Randomization

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 (SSD) for all subjects. The subject shall then be randomized to one of two groups:

a. Treatment Group, in which case the subject shall undergo device implantation on the scheduled implant date. These subjects shall go on to receive CCM treatment for 24 weeks as detailed below.

b. Control Group, in which case the subject will be followed with continued medical therapy for 24 weeks. For subjects randomized to the Control group, the scheduled implant date shall be cancelled but will still serve as the SSD.

3. Study Start Date/Optimizer Implantation

a. 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.

b. 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.

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 position and the other in the posterior position 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 position with a separation of at least ~2 cm.

Leads that are in place in subjects with a prior ICD and/or pacemaker implant will continue to be used for those devices, and may not be connected to the OPTIMIZER system. To ensure that the OPTIMIZER System does not interfere with proper functioning of the ICD or pacemaker, these devices shall be interrogated during application of CCM signals according to the device interaction testing procedure outlined in Appendix D. The main mechanism 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.

c. Predischarge (for Treatment Subjects)

When each of the implanted subjects is stable and suitable for hospital discharge, he or she will undergo a chest X-ray after the implantation and prior to hospital discharge and according to hospital policy to rule out pneumothorax and to evaluate lead placement.

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 subject has a pacemaker or defibrillator implanted, the pacemaker 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. At the discretion of the Investigator, the subject may be observed for an additional amount of time with CCM activated in the hospital prior to discharge.

Prior to discharge, subjects will be introduced to the battery charging system and provided a comprehensive overview on the use of this equipment.

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.

4. Week 2 Follow-up Visit

At 2 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 and an assessment for the occurrence of adverse events. For subjects randomized to the treatment arm, the OPTIMIZER generator will be interrogated to confirm proper functioning and parameters shall be adjusted as needed. In addition, the OPTIMIZER interrogation will include an assessment of the subject's compliance with battery charging to maintain CCM therapy ON. These subjects will also be further educated on the use of the OPTIMIZER System charger.

5. Weeks 12 and 24 Follow-up Visits

All subjects will return for follow-up at weeks 12 and 24 following the SSD. Each visit shall include an interim medical history, a medication review, a physical examination, an NYHA classification (blinded assessment), two CPX tests, a MLWHFQ, and an OPTIMIZER interrogation (for subjects with the device). The

OPTIMIZER interrogation will include an assessment of the subject's compliance with battery charging to maintain CCM therapy ON. The CPX test will be performed twice during both the 12 week and 24 week intervals, with the second test being performed between 1 day (24 hours) and 7 days after the first test. At 24 weeks, subjects will also undergo a 6MW test. The 6MW and CPX tests may be performed on the same day, but must be performed a minimum of 3 hours apart, with the CPX test performed first.

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 visit. If a subject randomized to device treatment becomes pregnant the device will be turned off. Any study subject who becomes pregnant will continue to be followed for evaluation of safety endpoints.

6. Post Study Follow-Up

Following the 24 week follow up visit, all subjects in the Control group and Treatment group subjects enrolled in Europe shall resume routine follow-up from their primary care providers and shall be discontinued from further active participation in the study. However, subjects will be contacted at ~6 month intervals to ascertain their vital status for up to 2 years from the SSD.

Subjects enrolled in the Treatment group in the United States can continue to receive CCM therapy and shall be seen at ~6 month intervals at the investigational site until FDA has made a determination of device safety and efficacy. These follow-up visits shall include a medical history, OPTIMIZER device interrogation and reporting of any OPTIMIZER device-related serious adverse events and deaths. In the event that the study is terminated prior to approval, or at the request of the subject, 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 subject in order to eliminate the possibility of further use of the device.

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

B. 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.

C. 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 peak VO_2 as assessed by cardiopulmonary stress test as evaluated by a blinded core lab. Subjects shall undergo 2 tests at each time point (baseline, 12 weeks and 24 weeks) and the average at each interval shall be the value used in the primary analysis. If only one test is performed or meets testing requirements for a particular interval, that single value shall be used in the analysis.

The secondary efficacy parameters shall include:

- Change in Quality of Life, as assessed by the Minnesota Living with Heart Failure Questionnaire

- Comparison of mean changes in peak VO_2 between groups with change in respiratory exchange ratio (RER) included as a covariate.
- 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.
- Comparison of mean change in peak VO_2 between groups that only includes tests on which RER is ≥ 1.05

Other efficacy parameters shall include:

- Comparison of mean changes in 6 minute hall walk test between baseline and 24 weeks
- Comparison of mean changes in VE/VCO_2 measured on CPX between baseline and 24 weeks.

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 baseline, 12 weeks and 24 weeks.

VIII. Assessment of safety

A. Specification of safety parameters

The safety of the OPTIMIZER System will be assessed by evaluating the incidence of OPTIMIZER device or procedure related complications (see section IX for statistical analysis). The primary safety endpoint shall be the proportion of subjects without experiencing either an OPTIMIZER device-related complication or a procedure-related complication by 24 weeks. The safety endpoint will considered to be met if the proportion of complication-free subjects is significantly larger than 70% (one-sided significance level of 0.025); equivalently, the safety endpoint will be met if the lower bound for the 95% confidence interval of the percent of subjects surviving without experiencing a primary safety event is not less than 70%.

Adverse events shall also be carefully recorded and compared between treatment and control groups.

An adverse event is defined as any undesirable change from the subject's baseline and usual health status (prior to their enrollment into the study) whether or not it is device or procedure related. An adverse event includes device failures that adversely affect the subject and/or require an intervention to correct the failure.

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

Adverse events that occur during this study may be associated with the OPTIMIZER implant procedure, or specifically associated with the use of the OPTIMIZER 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 (UADE) 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, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

For purposes of the primary safety analysis, an OPTIMIZER device or OPTIMIZER implantation procedure-related complication shall be any serious adverse event that is related to the device or the procedure as classified by the Events Adjudication Committee.

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 or Ethics Committee (EC) (as/if required according to IRB or EC 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 after the Investigator learns of the event. Impulse Dynamics will report UADEs to the DSMB, FDA and all reviewing IRBs and ECs as required.

After the 24-week study period, only deaths and OPTIMIZER device related SAEs shall be reported.

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/Ethics Committee approval.

IX. STATISTICAL CONSIDERATIONS

A detailed description of the statistical methods, sample size justifications and justifications for safety and efficacy parameters are provided separately in the Statistical Analysis Plan (SAP). Important features of the SAP are reviewed below.

A. Description of the statistical methods to be employed and justification of sample size

1. Primary efficacy analysis

   The primary efficacy analysis will compare differences in the change in peak VO_2 from baseline to 24 week follow-up visit between the Treatment and Control groups. An intent-to-treat analysis based on a Generalized Mixed-Effects Model will constitute the primary analysis as detailed in the Statistical Analysis Plan.

   The general statistical hypothesis to be tested is:

$$H_0: \beta_{int} \leq 0 \quad \text{vs} \quad H_A: \beta_{int} > 0$$

Where β_{int} is the coefficient for the interaction of time and treatment group and represents the difference in mean change in peak VO_2 24-weeks from baseline in the treatment vs. control groups. As will be detailed in the next section, a Bayesian approach will be employed to take advantage of the significant amount of data available from the original FIX-HF-5 study. Superiority of the treatment arm will be declared if the posterior probability that the mean change from baseline to 24-weeks in peak VO_2 in the prospective trial is higher in the treatment group (i.e., $\beta_{int}>0$) is 97.5% or higher, conditioned on the prospective data and the original FIX-HF-5 data.

Hierarchical Bayesian Design for Borrowing Data from the Original FIX-HF-5 Study for the Primary Efficacy Analysis

As noted above, the original FIX-HF-5 study did not meet the primary effectiveness endpoint of showing superiority of probability of response for the treatment group compared to the control group (average ITT imputation result of 38/215 = 17.7% Treatment responder versus 28/213 = 13.2% Control responder). However, in the subgroup of subjects with EF ≥ 25 subjects (which is the focus of the present study), a statistically significant increase in peak VO_2 was observed in Treatment versus Control.

FDA released the document "Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials" on February 5, 2010. This document explicitly allows sponsors to employ Bayesian designs in proposals to FDA, but lays out some important guidelines that must be satisfied. In particular, a Bayesian design must avoid putting strong priors on favorable outcomes as this will inflate type I error far above acceptable levels. In fact, Bayesian designs are required by this guidance document to conform to the same frequentist operating characteristics as traditional frequentist designs; usually this means requiring that the probability of a type I error will be kept very low. In order to be able to incorporate favorable prior information and yet not inflate type I error, the statistical model must be able to borrow in a flexible manner so that more borrowing is done when results for the prospective study are consistent with the favorable prior information but

relatively little borrowing is done when the prospective results are consistent with the null hypothesis. Hierarchical models are a natural approach to achieving this flexible borrowing strategy.

Statistical Model Used for Effectiveness

For a Bayesian design in this setting, we regarded the original study as having generated normally distributed longitudinal data in the 2 subgroups defined by EF ≥25 or <25. The current study will only enroll subjects in the EF ≥25 subgroup. If the favorable subgroup result holds up, then a fair amount of borrowing from this favorable subgroup should occur (but less than just pooling the prior and prospective subgroup data). If, on the other hand, the favorable subgroup is not confirmed than more borrowing will occur from the non-favorable subgroups in the previous study. The model used to achieve this is a hierarchical model consistent with one presented in Pennello & Thompson (Pennello G, Thompson L. Experience with reviewing Bayesian Medical Device Trials. J Biopharm Statistics. 2008;18:81–115). A detailed model description appears in the Statistical Analysis Plan. Inference for this model centers around the difference in mean changes in peak VO_2 between the treatment arm and control arm in the prospective data set conditional on *all* of the data both for the prior study (both subgroups) and prospective study (focused only on the single subgroup), and it will be required that the posterior probability of superiority be 97.5% or higher. The design simultaneously gives incremental power above and beyond that of a standalone analysis while preserving the low (5%) type I error of a standalone analysis.

Power, Type I Error Tables for Effectiveness and Sample Size

Operating characteristics for the Bayesian design are determined by simulating a large number of possible data sets for a variety of true values of the model parameters and then determining the associated posterior inference via Markov chain Monte Carlo methods (Lunn D J, Thomas A, Best N and Spiegelhalter D (2000) WinBUGS -- A Bayesian modelling framework: Concepts, structure, and extensibility. Statistics and Computing. 10, 325-337; Sturtz S, Ligges U, Gelman

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The type I error of the design is approximately 5%. More than adequate (86% or better) is ensured if the true interaction term (i.e. difference in mean change from baseline to 24 weeks for treatment vs. control arms) is at least 75% of that observed in the subgroup in the original study. Further details will be provided in the Statistical Analysis Plan

2. Primary Safety Analysis

The primary safety analysis shall evaluate the procedure- or device-related complication rates through 24-weeks of follow up. The statistical null hypothesis shall be that the proportion of patients in the treatment group without experiencing a primary safety event is less than 70%, and the alternative hypothesis shall be that the proportion is more than 70%. This lower limit of 70% was chosen to be the same criterion used in several prior studies of CRT (PMAs P010012: Contak CD CRT D, P030005: Contak Renewal TR, P030035: St. Jude Frontier, and P010012/S37: Contak Renewal 3AVT). Satisfying the primary safety endpoint will require rejecting the null hypothesis at a one-sided significance level of 0.025 using an exact binomial test. Equivalently, the endpoint will be met if the lower limit of the exact 95% confidence interval is above 70%. It is noteworthy that point estimate of freedom from this composite endpoint at 24-weeks among subjects in the subgroup EF≥25% was 88%.

3. Other efficacy analyses

Other efficacy analyses that will be analyzed in a hierarchical statistical method and will include:

a. MLWHFQ: Results will be analyzed both as a comparison between groups of the changes from baseline and as a responders analysis with a 10 point reduction in MLWHFQ considered as a "responder".

b. Between group differences in changes in mean peak VO_2 with RER included as a covariate in the analysis.

c. New York Heart Association (NYHA) classification by a blinded on site clinicians. Results will be analyzed both as a comparison between groups of the changes from baseline and as a responders analysis with a 1 class reduction in NYHA considered as a "responder".

d. An analysis of between group differences in changes in peak VO_2 that only includes tests whose RER is ≥1.05.

These analyses will be conducted on both the prospective data alone and on the prospective data pooled with the data from the original FIX-HF-5 study of the subgroup of interest (EF ≥25). Pooled models will include a study indicator to adjust for differences in overall success rate between studies. Analysis from the pooled data will constitute the analysis upon which success will be determined.

Since, with regard to efficacy, there are multiple hypotheses to be tested, the method of alpha control is the closed form hierarchical method. Thus in order to test endpoints beyond the primary endpoint, the primary endpoint must attain a posterior probability of superiority that exceeds the nominal value. This hierarchical approach does not result in additional inflation of the type I error rate. The two other efficacy parameters to be tested (changes in 6 minute hall walk test and VE/VCO_2) will not be included in the hierarchical statistical analysis described above.

B. Number of subjects planned to be enrolled

Based upon the power calculations above, 230 subjects will be randomized in a 1:1 ratio between the two groups.

C. Study Termination

The study shall be considered complete approximately 24 weeks after the last study subject is randomized, when all subjects have completed the Week 24 follow-up. Subjects enrolled in the US with an OPTIMIZER 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 perform 2 baseline measurements of peak VO_2 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 safety and efficacy endpoint assessment). An intent-to-treat analysis will be performed on the primary efficacy and safety endpoints and will include all subjects randomized, regardless of whether the subject withdrew prior to study completion. The main reason for withdrawal is anticipated to be a voluntary decision made by the subject to withdraw from the study. A Generalized Mixed-Effects Model will be performed for the primary analysis as detailed in the Statistical Analysis Plan (SAP). An analysis of missingness patterns between treatment groups will also be performed.

E. Procedures for reporting deviations from the original statistical plan

Any deviations from the original statistical plan will be submitted and agreed upon with the FDA prior to any implementation.

F. Selection of subjects to be included in the analyses

The primary analysis will be an intent-to-treat analysis and all subjects will be accounted for (See **Section IX.E**.).

X. DIRECT ACCESS TO SOURCE/DATA DOCUMENTS

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

XI. QUALITY CONTROL AND QUALITY ASSURANCE

Quality control and quality assurance is the responsibility of the Investigator and his/her study staff. Impulse Dynamics clinical representatives will provide training and support to ensure that data quality is optimal (accurate, valid, reliable, complete and reported in a timely manner). Data will be monitored in accordance with Impulse Dynamic's Monitoring procedures. Data used for publication will not identify the subjects, and publications will be generated in accordance with Impulse Dynamic's publication policy.

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/EC 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.

Amendments to the clinical investigation plan will include rationale for the amendment and will be approved by IRBs/ECs and the national competent authorities.

Deviations from the clinical investigational plan will be recorded and will be included in the final study report.

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 permissions including data entry, data viewing, data querying and data 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) or other privacy laws, as applicable.

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 as required for the study endpoints. The documents will be maintained in the Impulse Dynamics Clinical 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

Informed Consent Template /

HIPAA Template

Subject ID Number:___ - _____

Evaluation of the Safety and Efficacy of the OPTIMIZER System in Subjects with Moderate-to-Severe Heart Failure with Ejection Fraction between 25% and 45%: FIX-HF-5C

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. An 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 dependent on your randomization assignment described later in this informed consent form. You will be expected to come in for study assessments and procedures for approximately 7 months. This will include approximately one month for screening and

baseline testing with a six month follow-up period. If you receive an OPTIMIZER System implant, you will be asked to return for follow-up every 6 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 3 years. If you are in the Control group or in the OPTIMIZER group but not receiving the test therapy, you will be contacted at approximately 6 month intervals to check on your health status for up to 2 years following the start of your study participation.

Study Procedures

Certain medical tests and assessments will be performed to determine if you are eligible to participate in this study. These tests and assessments include:

- a physical examination
- an evaluation of your medications
- an evaluation of your medical history including all hospitalizations that have occurred in the prior year
- an assessment of your current heart failure symptoms
- an electrocardiogram (to check the electrical activity in your heart)
- an echocardiogram (to check the strength of your heart)
- a questionnaire that asks you about your heart failure symptoms
- a 24-hour Holter monitor test (a tape recording of your heart rhythm over the course of an entire day)
- two different types of stress tests. The first test is to see how far you can walk on flat ground for 6 minutes and the second test is performed on a treadmill while the oxygen in your breath is analyzed. You will repeat the test performed on the treadmill 1-7 days after the first test.

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.

In some cases, your doctor may be able to use an echocardiogram, 24-hour Holter, or electrocardiogram performed within 30 days prior to your consent to enroll in this study.

Many patients with heart failure develop a need for a device called an implantable cardiac defibrillator (ICD) and/or a pacemaker. If your doctor believes that you have a need for an ICD or pacemaker, this may be offer to you at this time.

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 Control 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.

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. The implantation is performed under sterile conditions on an exam table and an intravenous (IV) line is put into your arm. The IV delivers fluids and medication during the procedure. The medication will make you relaxed and drowsy but you will remain awake.

The implant includes three electrical wires (leads) that connect the main component of the OPTIMIZER System, the implantable pulse generator (IPG) to your heart through the veins inside your chest, very similar to procedures used when implanting a pacemaker device. The IPG is generally implanted under your skin in the shoulder area and contains a battery and components that deliver CCM therapy sealed inside. The leads are used to record the normal electrical signals generated by your heart and to deliver the CCM treatment to your heart. The skin is numbed prior to making an incision, and the leads are inserted and steered through the blood vessels into your heart while the doctor views them with moving x-rays.

Tests will be performed to ensure that the OPTIMIZER System and if you have one, the ICD System, are functioning properly. This test may require your doctor to make your heart beat quickly to see if your ICD will sense and properly treat that condition.

If you also have an ICD or pacemaker, 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 and the OPTIMIZER System will be turned on. 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. You will be discharged from the hospital, typically the day after the implant.

If you are randomized to the Control group, you will continue to receive optimal medical therapy and you shall receive the same study related assessments as detailed below.

All subjects follow-up (Optimizer group and Control group), will be asked to return to the hospital in two weeks after the beginning of the study for a medical history review. 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. You will also receive additional instruction on when and how to use the battery charger.

You will be asked to return for follow-up visits at 12-weeks and 24-weeks following your study start date. At these visits, you will undergo medication review, medical history, physical examination, OPTIMIZER device evaluation, completion of the questionnaire about symptoms you have during your daily life, an assessment of your current heart failure symptoms and two different types of stress tests. The first stress test is the 6 minute walk test and the second stress test is the treadmill test. You will repeat the treadmill test 1-7 days after the first test. 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 24-week visit. The OPTIMIZER System will be turned off in any subject who becomes pregnant.

Following the 24-week visit, 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 this case, a medical history and OPTIMIZER device interrogation will be performed at 6-month intervals until the FDA has completed its review of this study.

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

If you suspect that you have become pregnant while participating in the study, you must contact the study doctor immediately.

Risks Associated with the OPTIMIZER System Implant and CCM Treatment

The risks associated with implanting the OPTIMIZER System (which includes implantation of the pulse generator and the leads that connect the generator to your heart) and applying 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 the tricuspid valve, potentially resulting in tricuspid valve regurgitation
- damage to specialized tissue in the heart responsible for initiating each heart beat (i.e., the heart's c*onduction system*)
- transient ischemic attack (TIA) or stroke
- formation of blood clots
- chest wall sensations
- pain at the incision site
- infection
- collapsed lung
- a hole in the heart from the leads
- lead dislodgement
- fluid or blood accumulation around the heart
- death

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

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 is possible that the OPTIMIZER 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 suggests this is unlikely to occur. 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 heartbeat. 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. However, if you visit any other physician or medical center that needs to reprogram either of your implantable devices, please ensure that they are aware of possible interaction between the devices.

Risks associated with possible interaction between the ICD and OPTIMIZER charger

If in addition to the OPTIMIZER device, you also have an Implantable Cardioverter Defibrillator (ICD), there is the possibility that the ICD may inappropriately deliver therapy (shocks) if you place the charger wand over the ICD. Please make sure that you place the charging wand only over the OPTIMIZER implant site.

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. Malfunctions of system parts or other clinical circumstances (e.g., sepsis) may require corrective actions or possibly even surgical repair (repositioning, replacement, or removal) of the part or parts that are not working properly.

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 Subjects

There is a risk for all subjects 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 the following:

- 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. If researchers determine that there are benefits, then your participation in this research

study could benefit others who will suffer from heart failure in the future. However, because the therapy is not yet proven to be effective, you and others 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). So you can choose not to participate in the study 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, US FDA and other regulatory agencies 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.

FDA disclosure to all subjects in clinical trials

A description of this clinical trial will be available on http://www.ClinicalTrials.gov at the following link http://www.clinicaltrials.gov/ct2/show/NCT01381172 as required by U.S. Law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.

Compensation

The study sponsor will compensate you for your participation in the 24-week study according to the schedule listed below:

2-week follow-up visit:	$50
12-week follow-up visit:	$250
24-week follow-up visit:	$249

You will receive a single payment that includes compensation for each visit that you completed. You will be given that payment after the 24-week follow-up visit. If you end your participation in the study before to the 24-week visit or do not complete one or more of the visits listed above, you will still receive a single payment for each visit that you completed.

Reimbursement

During the 24-week study, if you live more than 50 miles away, you will be reimbursed for reasonable lodging, meals, parking fees and the transportation costs to and from the facility and your home. Reasonable lodging, meals and parking fees will also be reimbursed for subjects that require an overnight stay in order to complete the two treadmill stress tests required at the baseline visit, 12-week and 24-week follow-up visits. Car mileage will be reimbursed at the current IRS reimbursement rate per mile, which includes the cost of gasoline. You will be asked to maintain and submit expense receipts for reimbursement; reimbursement will be provided according to the study sponsor guidelines.

Costs

All costs related to the implantation of the OPTIMIZER System will be billed to your insurance provider. These costs include:

- The OPTIMIZER Device hospitalization
- The OPTIMIZER Device
- The OPTIMIZER Device procedure, including anesthesia
- Post implant chest x-ray

You and your insurance provider will be responsible for paying these costs including any co-pays, co-insurance or deductibles. If your insurance provider will not pay (denies payment) for the OPTIMIZER implant related expenses, the study sponsor will cover these costs directly.

You or your insurance provider may also be responsible for paying for any treatments or tests that your doctor orders for you if those treatments or tests are for standard, clinical care. You may have to pay for these tests if they are not covered by your insurance provider.

Neither you nor your insurance provider will be charged for any tests that are done solely for the purposes of this study other than the OPTIMIZER implant hospitalization as explained earlier.

The study sponsor will also cover the costs related to the removal of the device in the following circumstances:

- if you would like to leave the study and have the OPTIMIZER System removed
- if you would like to have the OPTIMIZER System removed at the end of the study
- if your OPTIMIZER System needs to be removed or replaced due to a device malfunction during your study participation

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._____. If you get ill or injured as the direct result of being in this study, the Sponsor will pay the costs for your medical treatment of the illness or injury only if it:

(a) Is directly caused by the study device;

(b) is not a medical condition that you had before you started the study;

(c) is not the result of the natural progress of your disease or condition;

(d) is not caused by your or the hospital's failure to follow the study plan or protocol; and

(e) is not proved to be directly caused by the negligence of a hospital employee. "Negligence" is the failure to follow a standard duty of care.

The Sponsor will not provide compensation for lost wages or for any other damages, expenses or losses, or for medical expenses that have been covered by your medical or other insurance.

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.

If you decide to withdraw from the study after starting to participate, we will keep the information we have collected up to that point, but we will not collect any additional information from you without your consent. We may, however, want to determine your vital status after you drop out of the study. To be able to determine your vital status (and if deceased, cause of death), we will consult sources of information such as the National Death Index.

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, the US FDA and other regulatory agencies to inspect my health data.

_____

Printed Name of Participant

_____ _____

Signature of Participant **Date**

_____ _____

Legally Authorized Representative (if applicable) **Date**

HIPAA Clinical Research Authorization

AUTHORIZATION TO USE AND DISCLOSE HEALTH INFORMATION

Evaluation of the Safety and Efficacy of the OPTIMIZER System in Subjects with Moderate-to-Severe Heart Failure with Ejection Fraction between 25% and 45%: FIX-HF-5C

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 FIX-HF-5C OPTIMIZER System 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 for the FIX-HF-5C Study

Data for this study will be recorded into data entry screens using the Medidata electronic data capture (EDC) system. 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
- Minnesota Living with Heart Failure Questionnaire
- Echocardiogram
- Cardiopulmonary Stress Test
- 6 Minute Walk Test
- 12-Lead ECG
- 24 Hour Holter Monitor
- Eligibility Determination
- Randomization
- Health Insurance Coverage

Implant Folder (for Subjects Randomized to the OPTIMIZER System):
- Implant Success
- Implant- OPTIMIZER and Lead Information
- Implant- Equipment Notes, & Personnel
- Discharge
- OPTIMIZER IVs Patient Training
- OPTIMIZER Interrogation

Follow-up Folders:

- Interim Medical History
- Follow Up Medications
- Follow-Up Physical Examination
- NYHA Classification
- Minnesota Living with Heart Failure Questionnaire
- Cardiopulmonary Stress Test
- 6 Minute Walk Test
- Pregnancy Test
- OPTIMIZER Interrogation (for subjects randomized to the OPTIMIZER System)

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
- Pre-Randomization Hospitalizations

APPENDIX D

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 System and the concomitant device. The following steps summarize the required testing:

1. Program the ICD so that it does not deliver antitachycardic therapy during this test.
2. Program the sensing windows of the OPTIMIZER and ensure that the OPTIMIZER System can be programmed to consistently delivery CCM therapy in the presence of the concomitant device.
3. 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.
4. 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.
5. 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.
6. Program the ICD to detect and convert an induced ventricular tachyarrhythmia. Program the OPTIMIZER 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 E

Follow-up of Subjects enrolled during the FIX-HF-5B Protocol

Background

FDA approved the FIX-HF-5B Confirmatory Study protocol in 2010 for the enrollment of 230 subjects at 30 US sites. The study was designed to prospectively evaluate CCM therapy in a subgroup of the pivotal trial (NYHA 3 and LVEF 25-35%) with the OPTIMIZER III System. A FIX-HF-5B protocol revision, version July 29, 2011 (G030099/S084), was approved by the FDA in August 2011 that included an expanded LVEF criterion of 25-45%.

Enrollment into the FIX-HF-5B Confirmatory Study started with the first subject consent on February 22, 2011. A total of 17 subjects were randomized from 2011-2012; 11 to the OPTIMIZER group and 6 to the Control group. The FIX-HF-5C Confirmatory Study enrollment began in 2013 with the next generation device, the OPTIMIZER IVs System.

Study Follow-up Procedures

Subjects enrolled into the FIX-HF-5B protocol shall continue follow-up per the current (FIX-HF-5C) protocol. The FIX-HF-5C protocol is a revision of the FIX-HF-5B protocol, with the study number change made primarily to delineate the difference in the index device implanted at the time. All FIX-HF-5B subjects are in the post-study follow-up phase and being seen every 3 months for a history and device interrogation.

OPTIMIZER III IPG Replacement:

FIX-HF-5B subjects requiring an exchange of their OPTIMIZER III implantable pulse generator (IPG) may receive the OPTIMIZER IVs IPG.

Consent Materials:

All FIX-HF-5B subjects have signed the current IRB-approved consent form for the FIX-HF-5B study. A template informed consent addendum is attached and should be provided to all FIX-HF-5B subjects currently in active follow-up.

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

FIX- HF-5C Clinical Report

1.1 Introduction

Clinical evidence to support approval of this PMA (M150003) is derived from FIX-HF-5 series of studies, including: the Phase I FIX-HF-5 Feasibility trial; the Phase II FIX-HF-5 Pivotal trial; and the FIX-HF-5C Confirmatory trial.

The Feasibility trial (FIX-HF-5, Phase I) examined the OPTIMIZER II System in patients with NYHA Class III or IV heart failure and a normal QRS duration. The results provided preliminary evidence of device safety and efficacy, which led to the conduct of the Phase II FIX-HF-5 Pivotal trial.

The Phase II FIX-HF-5 Pivotal trial was a prospective, randomized study that included 428 heart failure patients with NYHA functional class III-IV symptoms despite optimal medical therapy (OMT), ejection fractions (EF) $\leq$35% (or up to 45% per echo core lab reading) and QRS duration <130 ms. Patients were randomized 1:1 to either continue to receive OMT or received OMT plus CCM™ treatment delivered by the OPTIMIZER III device.

The primary effectiveness endpoint of the FIX-HF-5 study was ventilatory anaerobic threshold (VAT) evaluated by a blinded core lab and assessed by a responder's analysis. Comparisons between treatment and control in peak VO_2 and quality of life were statistically significant (p value 0.024 and <0.0001, respectively). More importantly, a post hoc sub-group analysis of patients with EF $\geq$ 25% showed significantly greater effect between the treatment and control groups for peak VO_2 and quality of life than in the cohort as a whole.

After consultation with FDA, Impulse Dynamics conducted an additional confirmatory study (FIX-HF-5C) with peak VO_2 as the primary effectiveness endpoint in patients with EFs ranging from 25% to 45% (inclusive). A Bayesian statistical approach was employed to take advantage of the data available from the FIX-HF-5 Phase II study. The FIX-HF-5C study was performed with the OPTIMIZER IVs device. It is important to note that at this point, the OPTIMIZER System was designated as an expedited access pathway (EAP) device on July 31, 2015, indicating that FDA believes the device fills an unmet clinical need and merits priority review.

The 160 patient FIX-HF-5C study forms the primary basis for this PMA and will be thoroughly described and discussed in this clinical report. Data from the FIX-HF-5 Phase II study are most relevant in that there was a pre-specified fixed borrowing of data from a subgroup of patients from this study for the Bayesian Analysis of the FIX-HF-5C primary endpoint: peak VO_2.

The results of the FIX-HF-5C study demonstrated a statistically and clinically significantly higher improvement in peak VO_2 in patients treated with CCM™ for 24 weeks in addition to OMT in comparison to patients treated with OMT alone. Similarly, quality of life as assessed by the Minnesota Living with Heart Failure Questionnaire (MLWHFQ), functional class (NYHA) and 6 minute walk were all shown to be statistically significantly better in CCM™-treated patients.

In parallel, the OPTIMIZER System has been available in Europe and Asia gaining real world experience. Investigator-initiated studies were conducted to examine long term effects of CCM™ (Kuschyk et al., 2015; Kloppe et al., 2016 and Liu et al., 2016). In addition, Impulse Dynamics conducted 2 registry studies (CCM-HF and CCM-REG) to further elucidate the use of CCM™ in the moderate-to-severe heart failure population.

Once enrollment was completed in the FIX-HF-5C study, a Continued Access Protocol (FIX-HF-5CA) was submitted and approved by the FDA. The first patient was enrolled in this study on July 3, 2017. The Continued Access Study utilizes the next version of the device, the OPTIMIZER SMART with the 3-Lead configuration. As detailed above, the switch to the OPTIMIZER SMART was necessitated due to OPTIMIZER IVs manufacturing constraints (i.e., loss of availability of the header material). The differences between the OPTIMIZER IVs and the OPTIMIZER SMART 3-Lead configuration are summarized above in Table 8; the main differences are the different epoxy material used for the header and the smoothness of the titanium can contour. Therefore, this PMA application is seeking approval for the OPTIMIZER SMART 3-Lead configuration device.

1.2 Clinical Need

CCM™ delivered by the OPTIMIZER SMART System provides a unique therapeutic modality for the treatment of patients with moderate to severe heart failure (HF), a life threatening and irreversibly debilitating disease for which there is an unmet clinical need.

1.2.1 Unmet clinical need

Despite major advances in drug and device therapies, heart failure remains a cause of substantial disability, hospitalizations, and mortality. There is a crucial need for additional safe and effective heart failure therapies, in particular in patients with normal QRS where there is currently no therapeutic medical device available in the United States. The OPTIMIZER SMART System fulfills an unmet medical need.

1.2.2 Life threatening and irreversibly debilitating disease

The heart is a life sustaining organ. When it fails, the heart can no longer supply adequate cardiac output to meet the body's metabolic needs, particularly during periods of exertion. Thus, heart failure (HF) is both a life threatening and irreversibly debilitating condition. Current statistics support this fact. Approximately 5.7 million people have heart failure in the United States according to CDC.[1] Fifty percent of people diagnosed with heart failure die within 5 years of diagnosis.[1] One in 9 deaths in 2009 included HF as a contributing cause[1]. In 2010, there were 1,801,000 physician office visits with a primary diagnosis of HF and 676,000 emergency department visits and 236,000 outpatient department visits for HF.[2] Clearly, morbidity and mortality are high in patients with HF. HF is life threatening since the likelihood of death is high unless the course of the disease is interrupted in patients before permanent damage is done. Moreover, heart failure can be considered irreversibly debilitating in that in

its moderate to severe stages, morbidity can have a substantial impact on day to day life of patients affected. Indeed, the patient population served by the OPTIMIZER device is characterized clinically as NYHA functional Class III and ambulatory IV. By definition, NYHA Class III patients have a marked limitation of physical activity but are reasonably asymptomatic at rest; less than ordinary physical activity causes fatigue, palpitation, or dyspnea in NYHA Class III heart failure patients. NYHA Class IV patients are even more impaired in that these patients have an inability to carry out any physical activity without symptoms; patients have symptoms at rest, which are increased with any amount of physical activity.

1.2.3 Lack of Alternative Therapies

Based on the above considerations, it is evident that the OPTIMIZER SMART is intended to treat a life threatening, irreversibly debilitating disease: heart failure. The OPTIMIZER SMART is the only available device that can provide CCM therapy.

CCM™'s target population is NYHA Class III and ambulatory IV subjects, with normal QRS duration and reduced ejection fraction despite appropriate, guideline-directed pharmacologic therapies. There are currently no device therapies available for this sub-group of patients.

Cardiac Resynchronization Therapy (CRT) is also indicated for patients with moderate to severe heart failure with prolonged QRS duration. CRT works by synchronizing the electrical activity of the heart and indirectly has an effect on ventricular chamber contractility. However, CRT is only indicated for patients with prolonged QRS duration, primarily those with QRS duration >150 ms. Since only ~30% of the patients with heart failure have a wide QRS[3], CRT is not applicable to 70% of heart failure patients. In addition, CRT applied to patients with systolic heart failure and a QRS duration of less than 130 ms may increase mortality[4].

Finally, patients with severe heart failure also have the treatment option of a left ventricular assist device (LVAD). However, even with newer and smaller devices being developed, LVADs are fraught with serious complications such as bleeding, stroke, infection, and thrombosis. Because of these risks, LVAD use is generally limited to patients with more severe heart failure than those qualifying for CCM™ therapy.

1.3 Intended Use and Indications for Use

Intended Use: The OPTIMIZER SMART System is intended to deliver CCM™ electrical signals to the myocardium of the heart.

Indications for Use: The OPTIMIZER SMART System, which delivers CCM therapy, is indicated for the treatment of NYHA Class III or ambulatory NYHA Class IV heart failure patients in normal sinus rhythm with LVEF ranging from 25% to 45% and QRS interval <130 ms to improve exercise tolerance, quality of life, functional status and reduce heart failure hospitalizations.

1.4 FIX-HF-5C

The FIX-HF-5C study received FDA approval on April 30, 2014 utilizing the then-current version of the OPTIMIZER family of devices, the OPTIMIZER IVs System. The investigation was initially limited to 40 sites and 230 subjects. The first patient was randomized on July 28, 2014. Through subsequent discussions with FDA, the OPTIMIZER system was granted expedited access pathway (EAP) designation on July 31, 2015. As a result, the final sample size for the FIX-HF-5C study was modified to 160 subjects; this was agreed upon with FDA on November 14, 2016. Enrollment was completed on February 28, 2017 and 24-week follow up for all subjects concluded in August 2017. The Continued Access Study phase of the FIX-HF-5C study was approved by FDA on April 6, 2017 and enrollment began July 3, 2017.

1.4.1 Overview of Study Design for FIX-HF-5C

FIX-HF-5C was a prospective, randomized, third-party blinded (CPX core lab), multicenter study. For the primary effectiveness endpoint, longitudinal data from the prospective study was analyzed together with 30% fixed borrowing of data from the 229 subjects with EF $\geq$ 25% from the FIX- HF-5 Phase II study using a Bayesian modeling approach. Subjects (n=160) were randomly assigned to one of two treatment groups with an allocation ratio of 1:1. Block randomization by site and etiology of heart failure (ischemic versus non-ischemic cardiomyopathy) was used to ensure balanced enrollment between the two groups.

1.4.2 Overview of Study Methodology

Sites identified potential patients from their clinic's chronic heart failure population. The target patient population consisted of subjects with ejection fractions from 25 to 45% (inclusive) whose symptoms were consistent with NYHA Class functional class III or ambulatory NYHA Class IV. Informed consent was obtained from potential subjects who were then enrolled in the study to undergo baseline screening testing to determine eligibility for the study. Baseline screening exams included: cardiopulmonary exercise testing (CPX) to determine peak VO_2, echocardiography to determine left ventricular ejection fraction (LVEF), 12-Lead ECG, 24-hour Holter Monitor, quality of life assessment (MLWHFQ), a blinded assessment of NYHA Class and 6 minute walk test. Each subject performed two CPX tests at baseline, and at the 12 week, and 24 week follow-up visits. The CPX tests were evaluated by an independent core laboratory. The core laboratory was blinded to the randomization assignment for individual patients.

If patients passed baseline testing, a device implant date was scheduled in the electrophysiology laboratory as soon as possible; this scheduled implant date served as the study start date (SSD) from which the timing of all future follow-up visits were determined. After passing baseline testing and meeting all entry criteria (Table 9), subjects were randomized in a 1:1 manner to either the Control Group that received

optimal medical therapy (OMT) alone or to the Active Group with OMT plus the OPTIMIZER IVs System. Subjects randomized to the Active Group were implanted with the device, and the implant date was canceled in subjects randomized to the Control group, but the putative implant date was kept as the SSD.

Table 9: Subject Eligibility Criteria

Inclusion Criteria
Subjects who are 18 years of age or older
Subject is male or non-pregnant female
Subjects have baseline ejection fraction >= 25% and <= 45% as determined by the echocardiography core laboratory
Subjects who have been treated for heart failure for at least 90 days (including beta blocker for 90 days)
Subjects who have NYHA functional Class III or IV heart failure
Subjects who have been receiving appropriate, stable medical therapy during the 30 days prior to enrollment (Stable is defined as no more than a 100% increase or 50% decrease in dose.)
Subjects have a pre-existing ICD or pacemaker system, if one is clinically indicated
Subjects who are willing to comply with the prescribed course of treatment and willing and able to return for all follow-up visits

Exclusion Criteria
Subjects whose baseline peak VO_2 is <9 or >20 ml O_2/min/kg
Subjects who have a potentially correctible cause of heart failure, such as valvular heart disease or congenital heart disease.
Subjects who have clinically significant angina pectoris, consisting of angina during daily life, an episode of unstable angina within 30 days before enrollment, or angina and/or ECG changes during exercise testing performed during baseline evaluation.
Subjects who have been hospitalized for heart failure which required the use of inotropic support within 30 days before enrollment.
Subjects who have a clinically significant amount of ambient ectopy, defined as more than 8,900 PVCs per 24 hours on baseline Holter monitoring.
Subjects having a PR interval greater than 375 ms.
Subjects who have chronic (permanent or persistent) atrial fibrillation or atrial flutter or those cardioverted within 30 days of enrollment.
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 perform baseline stress testing.
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.
Subjects who have a biventricular pacing system, an accepted indication for such a device, or a QRS width of 130ms or greater.
Subjects who have had a myocardial infarction within 90 days of enrollment

Exclusion Criteria
Subjects who have mechanical tricuspid valve.
Subjects who have a prior heart transplant.
Subjects on dialysis.
Subjects who are participating in another experimental protocol.
Subjects who are unable to provide informed consent.

Subjects then returned to the clinic for evaluation at 2 weeks, 12 weeks and 24 weeks following the initial implantation or SSD for control patients. At the 12-week visit, subjects completed 2 CPX tests, a blinded NYHA, MLWHFQ, a routine physical exam, a medical history and an assessment of adverse events. In addition to evaluations performed at the 12-week visit, the 24-week visit also included the 6 minute walk test. Data collection for assessment of the study endpoints was concluded with the 24-week visit. Table 10 provides the schedule of events for the study.

Table 10: Schedule of Events

			Follow-Up Schedule (relative to Study Start Date§)			Long-term F-up Every 6 Months** (relative to Study Start Date§)		
Test or Assessment	**Screening & Baseline**	**OPT Implant**	**Week 2 ±2 days§**	**+12±2 Weeks**	**+24±2 Weeks**	**US OPTIMIZER Group**	**US Control Group**	**EU OPT and Control**
Informed Consent	X							
1-Year Medical History/Interim History	X		X	X	X	X		
NYHA Class (site clinician assessment)	X			X	X			
Medications	X			X	X			
Physical Examination	X			X	X			
12-Lead ECG*	X							
24 hour Holter Monitor*	X							
Echocardiogram*	X							
MLWHFQ	X			X	X			
Cardiopulmonary Stress Test	2X			2X	2X			
6 Minute Walk Test	X				X			
Pregnancy test	X				X			
Eligibility determination	X							
Randomization	X							
OPTIMIZER System Implant		X						
Chest X-ray (prior to hospital discharge)		X						
OPTIMIZER Device Interrogation / Programming		X	X	X	X	X		
Adverse Events, Hospitalizations, and Procedures (as	X	X	X	X	X	X		

Test or Assessment	Screening & Baseline	OPT Implant	Follow-Up Schedule (relative to Study Start Date§) Week 2 ±2 days§	+12±2 Weeks	+24±2 Weeks	Long-term F-up Every 6 Months** (relative to Study Start Date§) US OPTIMIZER Group	US Control Group	EU OPT and Control
needed)/OPTIMZER device-related SAEs after 24-weeks								
Vital Status						X	X	X

§ Study Start Date (SSD): After completion and satisfying all entry criteria and prior to randomization, a date shall be scheduled for OPTIMIZER System implantation. This date shall serve as the start date for all subjects regardless of randomization assignment, from which all future follow-up visits are scheduled.

* 12-Lead ECG, 24-Hour Holter Monitor, and Echocardiogram test results (from the study-qualified lab) obtained within 30 days before informed consent and performed in accordance with the protocol, testing, and data collection requirements may be used for eligibility determination.

** US OPTIMIZER subjects are followed every 6 months (+/- 4 weeks) after the 24-week interval for device interrogation and reporting of OPTIMIZER Device related SAEs, if any. All other subjects are followed for vital status only, for 2 years following their SSD.

OPTIMIZER subjects in the US were then followed every 6 months at which time an interim medical history was obtained, device interrogation was performed, occurrence of adverse events was assessed, and vital status recorded. Control subjects and OPTIMIZER subjects OUS were assessed every 6 months for vital status only, until 2 years.

A detailed description of all study methodologies, associated criteria and definitions is provided in the Study Protocol for the FIX-HF-5C study (Attachment 4).

1.4.2.1 CPX Core Laboratory

We think it important to note that, to the best of our knowledge, no prior study has invested as much time, effort and financial resources to ensure the quality of every cardiopulmonary stress test (CPX). Quality measures taken in the FIX-HF-5C study, included: quality assurance testing at every site to validate equipment every 6 months; sending technicians to perform tests upon requests of the sites or when the core lab identified issues with test performance; mandating two tests at each timepoint; and rapid centralized reads of test quality and asking for additional tests when quality metrics were not met. Similar measures were taken in the FIX-HF-5 study with the exception of two tests at each timepoint. Thus, we believe that the data of the current study are valid, and reflect what can be expected from serial assessments of exercise tolerance in our target population.

Rigorous procedures were used for the conduct of CPX testing at the sites and the evaluation of the tests by a blinded core laboratory to optimize the quality of tests and achieve maximal effort from each patient. These measures included: 1) on-site training on standardized procedures for conducting CPX testing; 2) normal subject validation testing and revalidation every 6 months; 3) providing the patient with instructions on how to prepare for the CPX test; 4) rapid feedback on quality of every test from the core laboratory and retest requests for

inadequate tests; and 5) two tests performed at each time point.

Tests were deemed inadequate if: 1) the subject had an erratic or oscillatory breathing pattern; 2) the data were non-physiologic; 3) an issue was identified with the testing equipment; or 4) the test was submaximal, meaning it was terminated by either the subject or the supervising clinician/technician prior to the subject reaching volitional exhaustion. Reasons for early termination included non-heart failure symptoms (e.g., angina, heart rhythm disturbance, or leg, foot, or back pain) or the subject was technically challenged to perform the test.

Metabolic data were collected for 2 minutes prior to the start of exercise to confirm RER, VO_2, and the subject's ventilation volume were at normal, physiologic, and stable resting values before beginning the test. Metabolic data were then collected for the duration of the test and for an additional 2 minute recovery period following termination of the test. Peak VO_2 and peak respiratory exchange ratio (RER) were determined by the blinded core lab from averaged 20 second averaged gas exchange data from the start of exercise to the end of exercise. Tests were deemed to be of maximal effort if RER reached 1.05 or greater.

As noted, two CPX tests were performed for each subject at baseline and at the 12- and 24-week follow up visits. A 3rd test could be requested by the core lab if both tests were deemed inadequate based on criteria defined above. If both tests were deemed adequate, the average of the 2 tests was used for the value at that time point. If only 1 test was deemed adequate, then only that 1 value was used for the analysis. As in a prior study,[5] this approach was used to reduce variability of test results with the potential for reducing sample size.

The CPX core lab SOP is provided in Attachment 05.

1.4.2.2 Safety Oversight Committees

An Events Adjudication Committee (EAC) was established to review records of individual serious adverse events, hospitalizations and deaths. This committee was composed of 3 independent cardiologists experienced in the adjudication process. The committee provided definitions for OPTIMIZER device-related or procedure-rated complications, protocol-specified hospitalizations which included a hospital admission that resulted in a calendar date change or was related to an adverse event that caused a prolongation of the index hospitalization for device implantation. The committee also adjudicated the cardiac and heart failure relatedness of deaths and hospitalizations.

An independent Data and Safety Monitoring Board (DSMB) reviewed aggregate safety data and monitored for the emergence of any significant safety concerns. The DSMB was composed of 5 members with clinical trial experience in heart failure, electrophysiology and statistics not otherwise participating in the study.

The DSMB was unblinded to study group assignment.

1.4.3 Overview of Statistical Analyses

Statistical analysis of the FIX-HF-5C study data utilized two distinct statistical techniques. Analysis of the primary effectiveness endpoint, peak VO_2, was done using Bayesian techniques where fixed borrowing from the previous FIX-HF-5 trial was incorporated. The use of Bayesian methodology improved the statistical power of the results. The remaining effectiveness and safety endpoints were analyzed employing typical frequentist statistical methods. A detailed description of the Statistical Analysis Plan and the resultant Statistical Report for both Primary Effectiveness Endpoint and other endpoints can be found in the following attachments. We provide a brief overview here of the Statistical Methods.

Attachment 02 FIX-HF-5C Statistical Analysis Plan
Attachment 06 Primary Endpoint Analysis Specification
Attachment 07 Primary & Key Secondary Analyses Impulse Dynamics FIX-HF-5C
Attachment 03 Statistical Analysis Report of Impulse Dynamics FIX-HF-5C Study.

The primary effectiveness endpoint for the study was serial change in peak VO_2 measured at baseline, 12 weeks and 24 weeks of follow up. Here, we summarize the hypothesis for the primary analysis. Let Δ_3 be the mean difference in peak VO_2 between device and control groups at the third (24 week) visit, adjusting for baseline and 12-week peak VO_2 values. The primary analysis corresponds to a test of the following hypothesis:

$$H0 : \Delta_3 \leq 0 \qquad (1)$$
$$H1 : \Delta_3 > 0$$

A Bayesian model is fitted in order to obtain the posterior distribution of Δ_3. If the Bayesian posterior probability that Δ_3 is positive is greater than 0.975, i.e.

$$\Pr(\Delta_3 > 0) > 0.975 \qquad (2)$$

the null hypothesis will be rejected and the device will be considered superior to control with respect to the primary endpoint. As described in the analysis plan, the data from the FIX-HF-5 study that is incorporated into this Bayesian model is given by the following table:

Table 11: FIX-HF-5 Treatment Effect Posterior Distributions

Time	Posterior Mean	Posterior SE	Lower 95%	Upper 95%
12 weeks	0.232	0.343	-0.442	-0.908
24 weeks	1.080	0.344	0.413	1.759

As detailed in the statistical analysis plan (Attachment 02) and the final report on the Primary & Key Secondary Analyses Impulse Dynamics FIX-HF-5C (Attachment 07), the primary measure of effectiveness was defined as the change in peak VO_2 as evaluated by the blinded core laboratory. The primary analysis employed a Bayesian

repeated measures linear model to estimate group differences in mean peak VO_2 at 24 weeks from baseline, with 30% borrowing of information (70% down-weighting) from the corresponding treatment group difference observed in the FIX-HF-5 study subgroup.

More specifically, the Bayesian linear model incorporated peak VO_2 data from baseline, 12 weeks, and 24 weeks for each patient, in which a mean treatment difference was estimated at 12 and 24 weeks and set equal to zero (no treatment difference) at baseline on the premise of randomization. A random intercept was used to account for repeated observations within the same individual. An informative prior distribution was used for the treatment effect at 12 and 24 weeks based on FIX-HF-5 data, using the power prior methodology of Ibrahim and Chen[6], with a 30% weight or 70% down-weighting of the FIX-HF-5 subgroup treatment group difference. Non-informative prior distributions were specified for all other model parameters. The pre-specified primary analysis would conclude superiority of the CCM™ Treatment group versus Control if the Bayesian posterior probability of a positive treatment difference in favor of CCM™ treatment exceeded 0.975. In addition, a 95% Bayesian credible interval was provided based on the 2.5^{th} and 97.5^{th} percentiles of the Bayesian posterior distribution of the treatment difference. For summary purposes, and similar (non-Bayesian) repeated measures model was also fitted to the FIX-HF-5 and FIX-HF-5C studies (without borrowing) to summarize the treatment differences of each trial independently.

Quality of life assessed with the Minnesota Living with Heart Failure Questionnaire (MLWHFQ) was a key secondary effectiveness endpoint. The 21-question scale assesses the impact of the signature physical symptoms and signs of heart failure. Other questions look at physical and social functioning in the context of heart failure symptoms. Scores on the MLWHFQ can range from 0 to 105. The tool is validated for the heart failure patient population.

Additional secondary effectiveness endpoints include:

- Change in NYHA Class
- Change in Peak VO_2 including only tests with RER $\geq$ 1.05

The primary safety endpoint was the incidence of complications (OPTIMIZER device- or procedure-related serious adverse events that requires invasive treatment or results in a permanent disability or death). The success criterion for the safety endpoint was set such that the therapy would be considered safe if greater than 70% of the implanted population was free of such a complication. This criterion was agreed upon with FDA with approval of the final Data Development Plan (DDP) on July 13, 2017. Secondary safety endpoints included mortality, hospitalizations, and SAEs.

1.4.3.1 Analysis Populations

The primary analysis of effectiveness utilized the intent-to-treat (ITT) population, i.e., all randomized subjects. All subjects were analyzed in the group to which they were randomized. The analysis of the primary safety endpoint utilized the population of all

subjects implanted with the OPTIMIZER system. Supporting analyses of the primary endpoints were done in completed cases (CC) and the per protocol (PP) population. Secondary and additional effectiveness analyses were conducted in completed cases and the PP population. Completed cases refer to all available data for the particular endpoint of interest. The PP population is defined as subjects who received treatment (OPTIMIZER Group), have any follow-up post study start and have no protocol violations that would affect endpoint assessment. Secondary and additional safety endpoints were assessed in the PP population. The primary effectiveness endpoint was evaluated together with the borrowing of information from 229 subjects with EF≥25 from the original FIX-HF-5 study using a Bayesian modeling approach.

1.4.3.2 Subject Accountability

A summary table provides the total number of subjects screened, randomized and evaluable, by investigational site. The subjects eligible for and compliant with each follow-up visit were summarized descriptively. Subjects withdrawn were tabulated with their reasons for withdrawal.

Each subject screened for the study was accounted for. A subject accountability table presents the total number of screened and randomized subjects as well as the total number of evaluable subjects and subjects with a violation of specific inclusion or exclusion criterion. A tabulation of subjects who were screened but not randomized, and their reasons for ineligibility, is provided. Subjects who were ineligible at the intraoperative stage with the reason for ineligibility and subjects with a protocol violation with the specific violation are also listed. Subjects were grouped into broad categories for the purpose of tabulation.

1.4.3.3 Character of Study Variables

For continuous variables, the descriptive analyses present the mean, standard deviation, median, minimum and maximum. For categorical variables, the number with the characteristic, the total number evaluated, the percent and the 95% exact binomial confidence intervals are provided.

4.4.3.4 Comparability Analyses

Comparability analyses were performed to determine the similarity between treatment groups and study sites with respect to important demographic or other variables, either known or suspected to have an influence on the outcome variables. The absence of similarity for any variable identifies that variable as a potential covariate in subsequent safety and effectiveness analyses.

1.4.3.4.1 Treatment Group Comparability

The demographic and prognostic variables measured at study entry include baseline peak VO_2 between the OPTIMIZER treated and control groups. Continuous variables were compared with two-sample t-test or Wilcoxon rank sum test, and categorical variables were compared with Fisher's exact test or Chi-square test.

1.4.3.4.2 Study Site and Geographic Region Comparability

A set of important demographic or prognostic variables were compared across study sites to determine homogeneity of study sites in subject characteristics. Smaller study sites with insufficient numbers of subjects to allow a meaningful analysis were combined into one or more pseudo-sites to allow the comparison to be done. The size of any pseudo-site created in this way does not exceed the size of the study site with the largest enrollment

Demographic and prognostic variables were not used as a basis for combining data across study sites. Rather, the data were combined on a clinical basis, i.e., the sites used a common protocol, the sponsor adequately monitored the study to assure protocol compliance, and the data gathering and validation mechanisms were the same across all study sites.[7]

A sensitivity analysis was conducted on the primary outcome to determine if the estimated difference in treatments is consistent across pseudo-sites. A 3-level model with measurement occasions nested within subjects and subjects nested within pseudo-sites was performed to obtain an overall estimate of the combined treatment effect, allowing for the effect of treatment to vary over sites. Site by treatment interactions of a quantitative nature, i.e., all pseudo- sites show the treatment to be beneficial, but perhaps to a different degree by pseudo-site, were not considered to be an impediment to combining data. Site by treatment interactions that are qualitative in nature, i.e., the vast majority of pseudo-sites show the treatment to be beneficial, but one or more pseudo-sites show the treatment to be detrimental, requires extensive evaluation of the pseudo-sites with contrary results to attempt to determine what factors at those pseudo-sites led to the result.[8]

A similar sensitivity analysis was performed to compare a set of important demographic or prognostic variables across geographic regions (US vs non-US). A 3-level model with measurement occasions nested within subjects and subjects nested within study regions was performed to obtain an overall estimate of the combined treatment effect, allowing for the effect of treatment to vary between regions.

1.4.3.5 Primary Effectiveness Endpoint Analysis

The main effectiveness endpoints of the Impulse Dynamics FIX-HF-5 trial were ventilatory anaerobic threshold (VAT primary) and peak VO_2 (secondary) at 24 weeks, using multiple imputations to obtain estimates of missing data. In addition, responder analyses were conducted using a variety of arbitrary cut-points (i.e. percent improvement) as a basis for dichotomizing the quantitative data and "response rates" were compared between treated and control subjects. Results of these analyses showed that the effectiveness of the OPTIMIZER System, when assessed by increases in peak VO_2, is most evident in a subgroup of subjects with an EF>=25% at baseline.

Several issues were identified with the approaches used in the FIX-HF-5 study. First, they did not make full use of the available data, which included measurements at

baseline, 12, and 24 weeks. Second, in order to obtain an end-point, values had to be imputed for those subjects that had a missing value at 24 weeks. Third, the responder analyses were based on dichotomization of the underlying quantitative data using arbitrary thresholds which may not be clinically meaningful.

To overcome these limitations, the FIX-HF-5C study utilized an alternative statistical approach to the analysis of these data based on mixed effects regression models[9] with peak VO_2 as the primary endpoint. Unlike the 'pre-specified endpoint analyses using propensity score matching for imputation of missing data, the current analysis uses all available longitudinal data (baseline, 12 weeks, and 24 weeks from each subject). This statistical approach does not require imputation, but still provides the same level of robustness to missing values and drop-outs (missing at random - MAR)[10] employed by the previously used multiple imputation procedure. Specifically, we model the three repeated measures from each subject as normally distributed with arbitrary means. The correlation and variance parameter models used were chosen as those that give the best fit (by the Bayesian Information Criterion) to the FIX-HF-5 data. In particular, we found that an equicorrelation, equal variance model fit the data quite well, and was superior by BIC to:

(i) arbitrary variances and correlations;
(ii) random intercepts and slopes with arbitrary variances;
(iii) random intercepts and slopes with equal variances. Error variance was allowed to vary by study as the prospective data is expected to have lower variability due to averaging of replicated studies.

The primary effect of interest is the treatment by time-24-weeks interaction. A Bayesian approach was used (see next section) to extend this model to allow the treatment by time interactions to vary across the 2 subgroups and the 2 studies which allows the evidence in this new study to take into account the previous findings in FIX- HF-5.

As a sensitivity analysis with respect to pooling of centers, centers were dummy-coded and included as a fixed-effect in a model along with center by time, center by treatment and center by treatment by time interactions. If a significant center by treatment by time interaction is found at the p=0.15 level, then random center effects were included in a model which permits the treatment by time interactions to vary across centers, and the overall pooled estimate of the treatment by time interaction was obtained and tested for significance. This sensitivity analysis was based on FIX-HF-5C data only and was based on maximum likelihood methods (not Bayesian).

A similar sensitivity analysis was carried out to test for a region (i.e., US vs non-US) by treatment by time interaction.

Siddiqui, Hung and O'Neill of the FDA Office of Biostatistics conducted a detailed simulation study to compare the endpoint analytic approach of last observation carried forward (LOCF) to the generalized mixed-effects regression model that we have proposed here[11]. They conducted two extensive simulation studies to examine the empirical bias and Type I error rates associated with the estimators and tests of

treatment related effects under three missing data assumptions (missing completely at random (MCAR), MAR, and missing not at random (MNAR)). The results of these studies revealed that LOCF endpoint analysis can lead to substantial biases in estimators of treatment effects under all three of the missing data mechanisms evaluated, whereas the generalized mixed-model analysis of the available data leads to estimators with comparatively small bias, and controls Type I error rates at the nominal level in the presence of MCAR, MAR, and some cases of MNAR. In a sensitivity analysis of 48 RCTs from 25 NDAs, the generalized mixed model was the superior approach in controlling Type I error rates and minimizing biases as compared to the endpoint analytic approach. Interestingly, no evidence of MNAR was found in these real datasets.

1.4.3.5.1 Bayesian Primary Analysis for Borrowing Strength from the Original FIX -HF-5 Study

Specific details of the primary analysis, including relevant simulations and operating characteristics, are given in the "Primary Analysis Specification" report provided with the Primary Analysis Report (Attachment 06).

1.4.3.5.2 Supportive Secondary Analyses

As supportive analyses, we used a correlated repeated measures model identical to the primary analysis model to analyze the prospective FIX-HF-5C trial on a standalone basis. This model was based on maximum likelihood methods (non-Bayesian). We also used correlated repeated measures model to test for baseline factors that modify the relationship between the changes in peak VO_2 associated with the OPTIMIZER treatment. We did this for all possible clinically relevant variables including age, gender, baseline peak RER, baseline ejection fraction, history of diabetes, NYHA class per blinded assessment, primary heart failure etiology, pacing or ICD use, baseline Minnesota Living with Heart Failure questionnaire score, and study site. Potential covariates were screened by the method of Hosmer and Lemeshow.[12] The screening was done by forming bivariate regression models with treatment, the covariate, and the treatment by covariate interaction. If the interaction or the main effect has a p-value of 0.2 or less, the covariate was allowed to enter the competition for the final (secondary analysis) model. The final supportive model was done by manual backward elimination and retained only main effects and interactions that have a p-value of 0.025 or less. Recall that if an interaction is statistically significant, the main effects for the terms in the interaction must be included in the model regardless of their p-values.

As further supportive secondary analyses, the Bayesian modeling of the primary endpoint (with borrowing of FIX-HF-5 data) as well as the above standalone secondary analyses (no borrowing) was repeated for the CC and PP populations.

The results for these analyses are also found in the Primary & Key Secondary Analyses Impulse Dynamics FIX-HF-5C report (Attachment 07).

1.4.3.6 Primary Safety Analysis

The primary safety analysis evaluated the OPTIMIZER procedure- or device-related complication rates through 24-weeks of follow up. We constructed an exact binomial 95% confidence interval for the complication free proportion.

The primary safety endpoint was the percentage of subjects in the OPTIMIZER group who experienced either an OPTIMIZER device or OPTIMIZER procedure related complication through the 24-week follow-up period, as determined by an independent events adjudication committee (EAC). The EAC reviewed all serious adverse event reports (SAEs), confirmed the classification of "serious", and adjudicated the relationship of the event to the OPTIMIZER System device or procedure. SAEs that the EAC determined to be definitely related to either the OPTIMIZER System or the OPTIMIZER Procedure were further classified as either a Complication or Not a Complication. A "complication" is an OPTIMIZER device or OPTIMIZER procedure related event that requires invasive treatment or results in a permanent disability or death.

Satisfying the primary safety endpoint required that the complication-free proportion of the population was significantly higher than 70% (using a one-sided significance level of 0.025).

1.4.3.7 Justification of Sample Size

Power calculations for a longitudinal design are normally quite complex, and the addition of the Bayesian modeling increases the complexity. We adopted the following approach. Data were simulated based on a multivariate normal distribution, in which the means, variances, and correlations between time points are based on the FIX-HF-5 data. We assumed that all variance components for the prospective study were the same as their estimated values in the subgroup of interest analysis from the FIX-HF-5 data except we allowed the variances to be lower to reflect the 2 independent replicates being averaged together for each measurement, and we allowed this general covariance structure to be scaled smaller or larger than the FIX-HF-5 study. We also assumed that the control group means at each time point are the same as in the subgroup of interest for the original trial. We then simulated a large number of prospective datasets under these assumptions for a variety of possible true treatment effects (differences in change from baseline to 24 weeks between control and treatment arm) and calculated the proportion of these datasets that would satisfy the Bayesian superiority criterion of the previous section. Assuming a true treatment effect of O (that is the slopes in the two arms are identical) yields the type I error. Simulations are presented in the "Primary Analysis Specification" report (Attachment 06). For 30% borrowing of the FIX-HF-5 data, the Type I error was controlled at approximately 0.10, and has power ranging from about 0.40 for the smallest effect to 0.99 for the largest effect.

1.4.3.8 Secondary effectiveness analysis

If the null hypothesis was rejected for the primary endpoint, it was planned that the secondary effectiveness analyses would be performed. Details of the secondary effectiveness analyses are provided in the "Primary Endpoint Analysis Specification" report (Attachment 06) provided with the “Primary & Key Secondary Analyses Impulse Dynamics FIX-HF-5C” Report (Attachment 07).

1.4.3.9 Supporting Secondary Effectiveness Analyses

A supporting analysis of the secondary endpoints was done using the combined FIX-HF-5C and FIX- HF-5 subject data with baseline NYHA III-IV and baseline EF≥25% (to be referred to as the FIX-HF-5 Subset).

These supporting secondary effectiveness analyses were done in the completed cases population from the combined FIX-HF-5 Subset and FIX-HF-5C data sets. The analysis of MWLHF and peak VO_2 with RER ≥1.05 utilized a repeated measures analysis of variance restricted maximum likelihood model that included baseline value of the variable being analyzed, treatment group, study visit, and etiology used in the randomization. The NYHA analysis of at least one class reduction from baseline used the same Mantel-Haenszel method proposed from the secondary endpoint applied to the combined study groups.

1.4.3.10 Exploratory Effectiveness Analyses

As exploratory analyses, all primary and secondary analyses are repeated with pooled FIX-HF-5 Subset and FIX-HF-5C data using maximum likelihood methods, with adjustment for study where applicable (e.g. a fixed effect for study in longitudinal models).

A series of additional analyses of effectiveness were performed. Each variable was tested with a univariate and multivariate test. The univariate test for categorical variables were with Fisher's exact test and the multivariate analysis was done with logistic regression. If the variable is ordinal or continuous, the univariate test was a two-sample Wilcoxon rank sum test and the multivariate test was done with the analysis of variance procedure or equivalent. Screening for all multivariate analyses was done to prevent over specification of the model.

The additional analyses include:

a. Univariate and multivariate evaluation of the primary effectiveness endpoint in the per protocol population.
b. Comparisons of treatment effects separately in subjects whose CHF etiology is ischemic or non-ischemic.
c. Comparison of treatment effects separately in the subjects whose EF is ≥ 35%

d. Comparison of treatment effects in the subjects with NYHA Ill symptoms at baseline
e. Comparison of mean changes in 6 minute hall walk test between baseline and 24 weeks.
f. Comparison of mean changes in VE/VCO_2 between baseline and 24 weeks
g. A comparison of treatment effects between the lead types (i.e., St. Jude, Biotronik, and Boston Scientific) utilized during the FIX-HF-5C study were performed.
h. The number of days in and out-of-hospital was analyzed for each study for subjects with EF ≥25 and NYHA class of III or IV.

These analyses are supportive or exploratory analyses and are not intended to be part of claims for the device. Their purpose is to investigate properties of the device that may be used in publications or for planning additional claims in future studies.

1.4.3.11 Secondary Safety Analysis

The nature, frequency, and seriousness of adverse events between the two groups were compared using descriptive summary statistics. In addition, the primary safety endpoint and hypothesis were tested on the completed cases and per protocol populations.

- All-cause mortality
- Cardiac mortality
- Composite rate of all-cause mortality and all-cause hospitalization
- Composite rate of cardiovascular mortality and heart failure-related hospitalizations
- Overall incidence and seriousness of adverse events

Kaplan Meier plots and log-rank tests were used to descriptively compare treatment groups for each of the above outcomes. Summary statistics were presented for both the prospective data alone and on the prospective data pooled with the data from the original FIX-HF-5 study in the subgroup of interest (NYHA=III or IV, EF ≥25% subgroup).

1.4.3.12 Missing Data

Our primary approach to handling missing endpoint data was the mixed effects modeling framework. Mixed models provide valid inference for the model parameters provided that all missing data are "missing at random" (MAR) with respect to the data used in the statistical model. If the MAR assumption does not hold, inference can be biased. In particular, endpoint data missing due to patient death or to heart failure hospitalization are not MAR. To handle these specific cases a value of 0 was imputed if the reason for missing was death and the minimum value

observed from the cohort at the respective time point was imputed if the reason for missing was heart failure hospitalization. For all other cases, including events occurring between enrollment and start date, assumed to be MAR, there are several approaches we could potentially use to examine the sensitivity of our results to this assumption.[13] Our primary presentation employs a tipping point approach.[14] We constructed a grid showing the effect of filling in a range of pairs of values for missing control and treatment arm patients. The grid ranged from –2 SD's below the average (here SD means the standard deviation of the non-missing values of the outcome measure of interest) to 2 SD's above the average by increments of 0.1 SD's with one axis for treatment group and the other for control group. For each location in this grid, we filled in the indicated control and treatment values for all missing data points and then indicated whether our primary endpoint was met or not met by shading the grid box different colors. The grid can be thought of as a way to bridge quasi-continuously between a worst-case, most likely-case, and best-case analyses. In addition, we compared the patterns of missing data between the treatment and control group by constructing a two-way table of all possible missingness patterns (as there are 3 time points, there are 8 possible patterns) vs. study arm.

1.4.4 Protocol Deviations

Protocol deviations were reported from baseline testing through the end of the 24-week study period and are tabulated by category, study interval and randomization assignment in Table 12 below. There were no protocol eligibility deviations reported.

Table 12: Protocol Deviations Number of deviations (number of subjects)

	Baseline		SSD-24 weeks	
Deviation Category	**Control**	**Active**	**Control**	**Active**
Consent and re-consent	1	0	3(3)	3(3)
Medication reporting	1	0	0	0
Testing	1	2(2)	18(15)	18(15)
Implant not done			N/A	3(3)
dP/dt testing not done			N/A	2(2)
CCM therapy			N/A	1
Follow-up visit done out of window			22(20)	16(14)
2 week visit not done			3(3)	0
4 week visit not done			1	0
12 Week follow-up not done			2(2)	0
24 Week follow-up not done			5(5)	0
Subject Lost To Follow-up			0	1

	Baseline		SSD-24 weeks	
Deviation Category	**Control**	**Active**	**Control**	**Active**
SAE Reporting Delay	0	0	4(4)	2(2)

Consent and re-consent: The deviation related to consent at baseline was because the consent process was not documented in the medical record. The 6 follow-up re-consent deviations were for either a delay in providing a revised version of the consent form or an extra consent addendum was incorrectly provided to the subject in addition to the main consent form.

Medication reporting: One subject did not have complete reporting of the baseline medications.

Testing: This includes individual tests that were done outside the protocol window, were not done at all, the equipment failed during the test, or the test was not done in accordance with the testing procedure.

Implant not done: Subjects that were randomized to the OPTIMIZER System but did not receive the device are described in detail in another section of the current report.

dP/dt testing not done: The September 25, 2015 version of the protocol dropped the requirement of dP/dt testing that involved performing a left heart catheterization in the patient prior to implanting the device. Two (2) implant cases were done after FDA approval with IRB approval documentation pending.

CCM™ therapy: Subjects are typically discharged with CCM™ therapy programmed ON after the index hospitalization. In one case, due to lasting effects from the anesthesia, CCM™ was initiated 2 days later.

Follow-up visit done out of the window: This included study visits that were completed but were done either prior to the study window start date or after the study window end date.

2 week or 4 week visits not done: Four visits were not done in Control group subjects. These study visits only required a safety assessment and an OPTIMIZER device interrogation for subjects that received the device. Control subjects that did not return for these visits were assessed for safety over of the phone until they returned for the 12-week visit. No effectiveness endpoints were required at these two intervals.

12 week or 24 week visits not done: As with the 1 and 4-week visits, the 12 and 24 week missed visit deviations were only reported in the Control group. There were 7 subjects that missed either the 12 week or the 24 week visit.

Subject Lost To Follow-up: There was one subject that was randomized but was never heard from again after that. The details of this case are described in the Subject Accountability Section of the current report.

Study visits performed outside the study window specified in the protocol accounted for a majority of the protocol deviations that occurred. None of the protocol deviations were serious enough to cause the associated patient to be removed from the overall

analysis of data. Similarly, none of the protocol deviations were judged to have a significant impact on the outcomes achieved in the study, either positive or negative.

The majority of the "Testing" deviations had to do with the subject being unable to do, or refusing to do, the CPX testing at one or both follow-up intervals. All have been detailed below for each study group.

There were 18 testing deviation reports in 15 Active subjects.

1. Subject 06-404 (Active, 2 Test Deviations) did not do the CPX testing at 12 or 24 weeks, due to back pain with ambulation. At the 24 week interval, the subject also did not do the 6MW test.
2. Subject 06-409 (Active, 1 Test Deviation) did the 24 week NYHA assessment out of window (2 days late) due to the blinded NYHA coordinator being unexpectedly out of the office on the scheduled visit day.
3. Subject 32-409 (Active, 1 Test Deviation) was unable to have the OPTIMIZER device interrogated due to a lead dislodgement.
4. Subject 51-426 (Active, 1 Test Deviation) did the 6MW test 73 minutes after completing the CPX test, when the SOP requires a 3 hour period between the 2 tests.
5. Subject 51-456 (Active, 1 Test Deviation) only did one 12-week CPX test and was unable to do the second one due to his wife dying that week.
6. Subject 51-459 (Active, 1 Test Deviation) performed several of the required 12-week assessments 4 days prior to the visit window starting, including one of the two required CPX tests. The second CPX test was performed within the study window.
7. Subject 57-413 (Active, 1 Test Deviation) did the 6MW test prior to the 3 hour period required after completing the CPX test.
8. Subject 65-403 (Active, 1 Test Deviation) did not have a 12-week NYHA assessment done, due to a scheduling oversight.
9. Subject 70-410 (Active, 1 Test Deviation) did the 6MW test prior to the 3 hour period required after completing the CPX test.
10. Subject 72-406 (Active, 1 Test Deviation) did the NYHA assessment outside the 24-week study visit window (44 days late).
11. Subject 75-429 (Active, 2 Test Deviations) refused to complete the 12-week and 24-week CPX testing due to symptoms of nausea experienced after test.
12. Subject 78-401 (Active, 1 Test Deviation) only did one 24-week CPX test. Test #2 could not be done do to a hardware failure of the equipment.
13. Subject 90-405 (Active, 1 Test Deviation) did not have a pre-discharge x-ray taken as required per protocol.
14. Subject 90-406 (Active, 1 Test Deviation) did not have a pre-discharge x-ray taken as required per protocol.
15. Subject 90-422 (Active, 2 Test Deviations) performed both 12-week CPX tests as required, however due to an equipment malfunction, the data from test #2 was lost. This subject completed all testing required for the 24-week interval, however the

6MW test and the MLWHFQ were done outside of the protocol visit window (9 days late).

There were 18 testing deviation reports in 15 Control subjects.

1. Subject 08-401 (Control, 1 Test Deviation) completed the 12-week visit, including CPX test #1, within the study window. The second of the 2 required CPX tests was canceled due to weather and not performed until 28 days later. Only test #1 was approved by the core lab.
2. Subject 41-405 (Control, 2 Test Deviations) refused to do CPX testing at 12 weeks and 24 weeks. At the 24 week visit, the subject also refused to do the 6MW test and NYHA assessment
3. Subject 51-432 (Control, 1 Test Deviation) only did one 12-week CPX test and refused to do the 2nd one.
4. Subject 51-438 (Control, 1 Test Deviation) only did one 24-week CPX test and did not do the 2nd one due to his travel schedule.
5. Subject 51-467 (Control, 1 Test Deviation) did not do the 24-week CPX or 6MW testing due to a recent pulmonary embolism. All other tests and assessments were performed.
6. Subject 55-408 (Control, 1 Test Deviation) had a foot fracture and was on continuous oxygen therapy and was unable to do CPX testing at the 12-week interval.
7. Subject 55-413 (Control, 1 Test Deviation) became ill after the 1st CPX test for the 24-week interval, so the 2nd test was not performed.
8. Subject 59-408 (Control, 1 Test Deviation) did not do the 24-week 6MW test due to a scheduling oversight and it wasn't realized until the testing widow had closed.
9. Subject 65-421 (Control, 2 Test Deviations) refused to complete the 12-week CPX testing and also refused the 24-week CPX testing due to orthopedic issues.
10. Subject 65-431 (Control, 1 Test Deviation) did not complete the 12-week CPX testing due to his traveling schedule.
11. Subject 65-450 (Control, 1 Test Deviation) did the 6MW test prior to the 3 hour period required after completing the CPX test.
12. Subject 65-475 (Control, 1 Test Deviation) performed both 24-week CPX tests as required, however due to an equipment malfunction, the data from test #2 was lost.
13. Subject 70-411 (Control, 1 Test Deviation) refused any study specific testing during 12-week visit except for the MLWHFQ and NYHA assessment.
14. Subject 75-424 (Control, 1 Test Deviation) only did one 12-week CPX test and refused to do the 2nd one.
15. Subject 90-408 (Control, 2 Test Deviations) did not perform the 12-week CPX testing or the 24-week 6MW test and CPX testing due to a diabetic foot ulcer.

Table 13: Testing Deviation Summary

Testing Deviation	Control Group	Active Group
Pre-discharge x-ray no done	N/A	2

OPTIMIZER Interrogation not done	N/A	1
No CPX testing at 12-weeks	4	2
Only 1 CPX test done at 12-weeks	4	2
No NYHA assessment at 12-weeks	0	1
No CPX testing (or 6MW) test at 24-weeks	5	2
Only 1 CPX test done at 24-weeks	2	1
No 6MW test at 24-weeks	1	0
Time between CPX test and 6MW test too short	1	3
Testing done late outside of protocol window	1	3
Testing done early outside of protocol window	0	1
	18 (15)	**18 (15)**

1.4.5 Ethics Statement

The study followed the Declaration of Helsinki and adhered to good clinical practices as defined in ICH-E6.[15,16]

1.4.6 Results

The following section summarizes the results of the FIX-HF-5C study and discusses the clinical implications of those results for the safety and effectiveness of the OPTIMIZER IVs and thus, OPTIMIZER SMART 3-Lead configuration, systems. Further detail concerning the statistical aspects of analyses presented are provided in Attachments 03 and the Primary & Key Secondary Analyses Impulse Dynamics FIX-HF-5C (Attachment 07).

1.4.6.1 Study Enrollment

There were 488 subjects that signed informed consent; 480 of those subjects were screened for the study and 160 were randomized**.**

Table 14 below provides a listing of all participating study centers with the number of patients screened and ultimately randomized to the OPTIMIZER or Control group for the study.

Table 14: Distribution of Subjects by Treatment Group and Study Site

Site Number and Name	Screened[1]	Control n(%)[2]	OPTIMIZER n(%)[2]	Total Randomized
06 The Ohio State University	10	3 (50.00)	3 (50.00)	6
08 Stern Cardiovascular Foundation	8	3 (75.00)	1 (25.00)	4
09 Christus Mother Frances Hospital	17	2 (50.00)	2 (50.00)	4
15 Aurora Research Institute	4	1 (100.00)	0 (0.00)	1
21 The Detroit Medical Center	13	1 (50.00)	1 (50.0)	2

Site Number and Name	Screened[1]	Control n(%)[2]	OPTIMIZER n(%)[2]	Total Randomized
31 Advocate Medical Group	6	0 (0.00)	0 (0.00)	0
32 Ochsner Clinic Foundation	12	2 (50.00)	2 (50.00)	4
36 lnova Research Center	4	2 (100.00)	0 (0.00)	2
41 Bryan Heart	8	2 (66.67)	1 (33.33)	3
51 VA Dallas Medical Center	68	15 (53.57)	13 (46.43)	28
54 Donald Guthrie Foundation	20	2 (50.00)	2 (50.00)	4
55 Baptist Health Lexington	16	2 (33.33)	4 (66.67)	6
56 Spartanburg Regional Medical Center	5	1 (50.00)	1 (50.00)	2
57 AZ Heart Rhythm Center	24	3 (60 .00)	2 (40.00)	5
58 Florida Hospital Cardiovascular Institute	1	0 (0.00)	0 (0.00)	0
59 Yale University	8	1 (100.00)	0 (0.00)	1
60 Nebraska Heart Institute	1	0 (0.00)	0 (0.00)	0
61 The Lindner Center	1	0 (0.00)	0 (0.00)	0
63 University of Arizona	3	0 (0.00)	0 (0.00)	0
64 University of Maryland	1	0 (0.00)	0 (0.00)	0
65 Cardiovascular Associates of Mesa	80	13 (52.00)	12 (48.00)	25
67 Washington Adventist Hospital	3	0 (0.00)	0 (0.00)	0
69 Orange County Health Institute	1	0 (0.00)	0 (0.00)	1
70 Na Homolce Hospital	27	3 (75.00)	1 (25.00)	4
71 Asklepios Kliniken	9	2 (100.00)	0 (0.00)	2
72 University Medical Center Mannheim	8	1 (33.33)	2 (66.67)	3
74 Heart and Vascular Center Bad Bevensen	3	0 (0.00)	1 (100.0)	1
75 Universitat Göttingen	37	5 (45.45)	6 (54.55)	11
76 Charité University Hospital Berlin CVK	5	1 (100.00)	0 (0.00)	1
78 University of Munich (Großhadern)	1	0 (0.00)	1 (100.0)	1
79 Charité Campus Benjamin Franklin	4	0 (0.00)	1 (100.0)	1
80 UKSH (Kiel)	2	0 (0.00)	0 (0.00)	0
88 Cardiovascular Consultants	14	2 (66.67)	1 (33.33)	3
89 Pima Heart	11	2 (66.67)	1 (33.33)	3
90 Chan Heart Rhythm Institute	53	16 (50.00)	16 (50.00)	32
Grand Totals	488	86(53.75)	74(46.25)	160

Program: Create Patient Data.sas

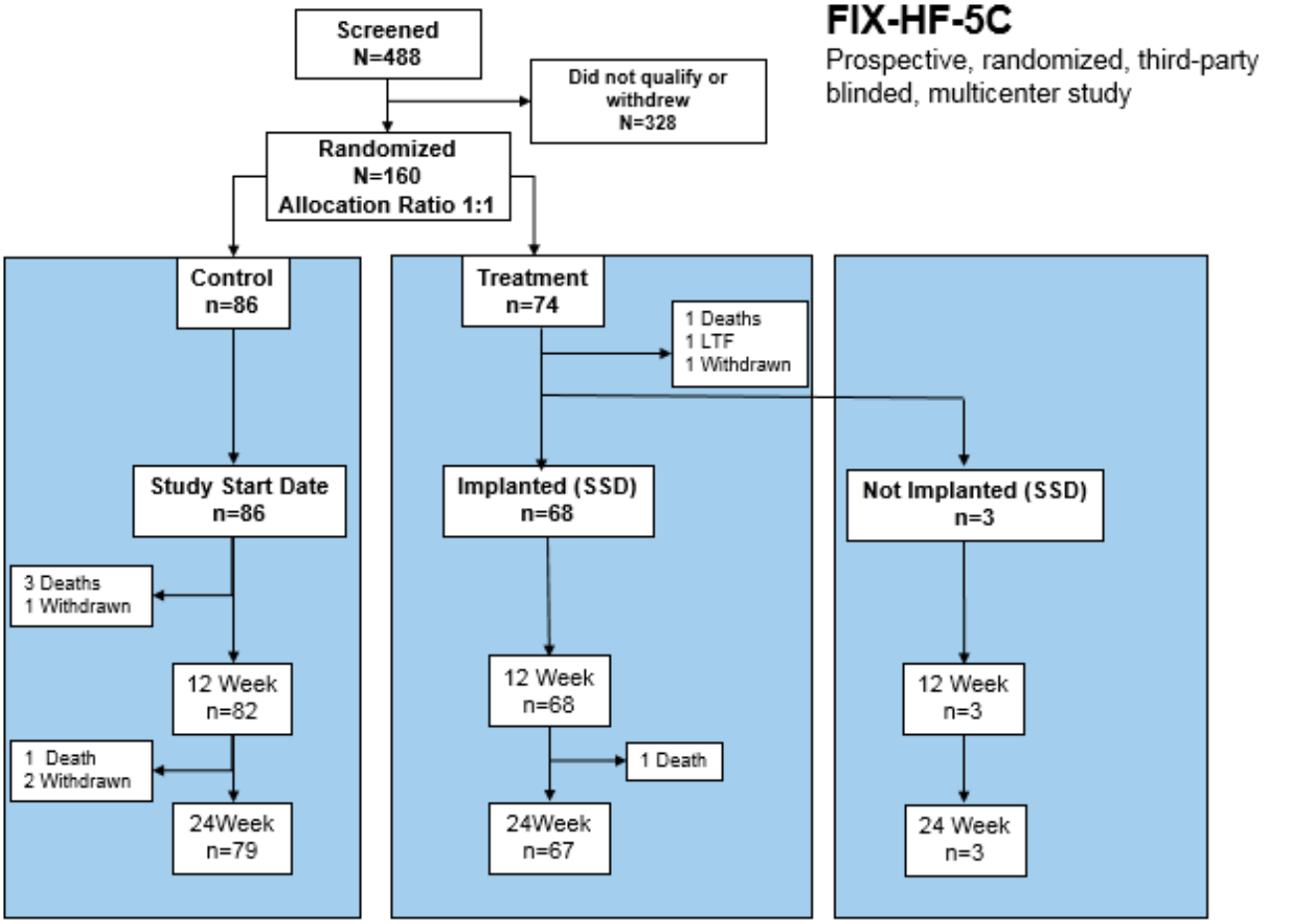
[1] Of the 488 subjects, 8 subjects did not get screened, and 314 subjects failed inclusion/exclusion criteria at screening. 166 passed the inclusion/exclusion criteria at screening, 3 of these subjects withdrew from the study prior to randomization, 3 subjects failed criteria other than those at screening, and 160 were randomized

[2] Percentage taken from the site total.

Nine of the 35 sites were OUS and accounted for 24 of the 160 (15%) randomized subjects. The three sites with the most subjects randomized into the study were: Dallas VA Center, Cardiovascular Associates of Mesa and Chan Heart Rhythm Institute. These three sites accounted for 85 (53%) of the 160 subjects randomized.

1.4.6.2 Subject Accountability

Figure 14 below illustrates the flow of subjects through the FIX-HF-5C study.



At the end of the 24th week both treatment and control group subjects were followed every 6 months.
During the follow-up the control group was assessed for vital status only and the treatment group was assessed to obtain vital status, interim medical history, AE incidence and device information.
*n=number of subjects

Figure 14: Flow of Subjects through FIX-HF-5C study

There were 488 subjects consented for the FIX-HF-5C study; 160 were randomized and 328 were not randomized. Table 15 lists the reasons for protocol exclusion for each of the 328 subjects. Investigators were asked to review the patient medical records for obvious exclusion criteria, such as the presence of a CRT, LVAD or heart transplant or QRS duration > 130 ms, before scheduling the patient for baseline testing. Baseline testing included 12-Lead EKG, 24-Hour Holter Monitor, and Echocardiogram and tests performed for clinical care purposes and done within 30 days before informed consent could be used for protocol eligibility

determination.

Table 15: Summary of reasons for study exclusion

# of Subjects	Primary reason for study exclusion
106*	pVO_2 >20
69**	LVEF < 25%
27*	Submax CPX testing
26	Subject withdrew
19*	Exercise limited
18	NYHA < Class III
13**	LVEF >45%
10	QRS ≥ 130ms
8	More than 8,900 PVCs on 24-Hour Holter Monitor
6	CRF revision due to protocol revision
5	Baseline medications not stable
5	CRT
2	Mitral valve related
2	Too healthy
1	Atrial fibrillation
1	Comorbidities
1*	CPX test inadequate
1	Participating in another research study
1	Incomplete testing, overall study protocol enrollment completed
1	MI within 90 days
1	Died prior to randomization
1	Subject non-compliance with baseline testing schedule
1	Subject too sick and unstable
1*	Unable to determine LVEF
1	Unstable heart failure
1	Venous Occlusion

*The majority of the reasons for exclusion were related to CPX testing or exercise limitations, with the majority of those due to a peak VO_2 >20.
**The second highest reason for exclusion was due to echocardiography testing. LVEF was >45% in 13 subjects, <25% in 69 subjects, and indeterminate in 1 subject.

Of the 160 subjects randomized in the study, 86 were randomized to the control group and 74 were randomized to the OPTIMIZER group. This imbalance in patient numbers was a chance occurrence due to the nature of block

randomization by site and CHF etiology.

1.4.6.2.1 Control Arm of the Study (Optimal Medical Therapy)

Eighty-six (86) subjects were randomized to the control group; 79 of the 86 subjects completed the 24-week study. Three (3) control subjects died prior to the 12-week visit (subjects 90-402, 65-427, 65-422) at 4, 36, and 70 days respectively. The causes of death included 2 pump failures and 1 death following a VT-ablation procedure. Another control subject (72-408) died after the 12-week visit and prior to the 24-week visit at 117 days, due to a pulmonary complication following a non-cardiac procedure.

Table 16: Summary on Cause of Death

Subject	Time	Cause of Death
90-402	Day 4	Pump Failure
65-427	Day 36	Pump Failure
65-422	Day 70	VT ablation procedure
72-408	Day 117	Pulmonary Complication following a non-cardiac procedure

One control subject withdrew prior to the 12-week visit (subject 88-407) at 77 days and 2 subjects withdrew after the 12-week visit and prior to the 24-week (70-411 and 71-401) visit at 86 and 115 days respectively.

Completed case report forms for control and OPTIMIZER treatment patients who died or were lost to follow up are found in VOL_007 and VOL_008 of this submission.

1.4.6.2.2 OPTIMIZER Treatment Arm of the Study

Seventy-four (74) subjects were randomized to the CCM™ Treatment group; 68 of these 74 subjects underwent device implantation. Six (6) subjects did not receive an implant. One (subject 65-446) died 2 days prior to the scheduled implant date, 1 (subject 57-409) was lost to follow-up prior to the scheduled implant date, 1 (subject 08-407) was deemed ineligible (interim assessment classified this patient as NYHA Class II) and was withdrawn, 1 (06-404) was discovered to have an additional abandoned ICD lead and the implant was canceled (follow-up testing through 24-weeks performed) and 2 subjects (subjects 51-423 and 51-454) elected not to undergo the implant procedure but follow-up testing through 24-weeks was performed. Thus, 3 of the six patients randomized to CCM™ treatment who did not undergo device implantation completed the 24-week study follow up visits.

In addition to the subject that died just prior to the implant date, 1 subject (88-402) died 164 days after the OPTIMIZER implantation due to sepsis following

surgery for an incarcerated hernia.

Narratives for lost to follow up (LTF) subjects and subjects who died are found in Attachments 08 and 09.

1.4.6.2.3 Visit Accountability

Table 17 illustrates the subject accountability and shows the study visits achieved within the window for the OPTIMIZER and Control groups.

Table 17: Subject accountability and Study visit for OPTIMIZER and Control Group

Interval	Implant/Study Start Date (SSD) x/n (%)	Week 12 x/n (%)	Week 24 x/n (%)
CONTROL			
Enrolled	86	86	86
Died[1]	0	3[5]	4[5]
Withdrawn[1]	0	1[6]	3[6]
LTFLJ [1 2]	0	0	0
Eligible[3]	86/86 (100.00)	82/86 (95.35)	79/86 (91.86)
Visit in Window	NA	72/82 (87.80)	67/79 (84.81)
Visit Outside Window	NA	8/82 (9.88)	10/79 (12.66)
No Visit	NA	2/82 (2.44)	2/79 (2.53)
OPTIMIZER			
Enrolled	74[4]	74[4]	74[4]
Died[1]	1[5]	1[5]	2[5]
Withdrawn[1]	1[6]	1[6]	1[6]
LTFLJ [1 2]	1	1	1
Eligible[3]	71/74 (95.55)	72/74 (97.30)	71/74 (95.95)
Visit in Window	71/71 (100.00)	65/72 (90.28)	64/71 (90.14)
Visit Outside Window	0 (0.00)	6/72 (8.33)	6/71 (8.45)
No Visit	3/74 (4.05)	1/72 (1.39)	1/71 (1.41)

Program: Create Patient Data.sas

[1] Deaths, intervention, withdrawn subjects, and LTFU subjects are cumulative over time.

[2] Lost to Follow-up

[3] The number eligible is the number enrolled minus the number that died and the number that withdrew or were intervened except for discharge. For Discharge examination, the subject had to have had an implant attempt (0 Control subjects and 58 OPTIMIZER subjects.

[4] Six OPTIMIZER subjects did not get an implant: subject 05-404 RCW had an abandoned lead that could not be explanted, subject 08-407MAJ improved and was no longer eligible, subject 51-423 M-W refused implant, subject 51-

454 MJP was a clinician decision due to health status of subject, subject 57-409 GJD was the LTFU who did not return after randomization, and subject 55-445 GDN died prior to implantation.

[5] Control subjects 55-422 RTH, 55-427 BAC, and 90-402 M-O died prior to the 12-week visit and subject 72- 408 HHH died prior to the 24-week visit. OPTIMIZER subject 55-445 GDN died prior to implant and subject 88-402 SET died prior to the 24-week visit.

[6] One subject assigned to the Control (88-407 WMR) withdrew prior to the 12-week visit and two Control subjects (70-411 M-K and 71-401 XXX) withdrew before the 24-week visit. One subject assigned to the OPTIMIZER (08-407 MAJ) improved and was no longer eligible for the study after randomization but prior to the discharge visit.

Table 18: Withdrawn Subjects with Reason for Withdrawal by Study Group

CONTROL		
Subject	**Study Days[1]**	**Reason for Discontinuation or Withdrawal**
70-411 M-K	86	Subject withdrew from the study without providing a reason. No further information is available.
71-401 XXX	115	Subject withdrew from the study during phone call with investigator, but the reason for withdrawal was not provided and no further information is available.
88-407 WMR	77	A physician treating the subject, but not involved as an investigator in the study protocol, advised the subject to withdraw from the study. No reason for withdrawal was provided.
OPTIMIZER		
Subject	**Study Days**	**Reason for Discontinuation or Withdrawal**
08-407 MAJ	0	Due to time lapse between randomization and implant, an improvement of health status was noted (NYHA III to NYHA II) and the subject was no longer eligible.

Program: Create Patient Data.sas

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

1.4.6.3 Analysis Populations

The following subjects are excluded from per-protocol analyses along with reasons for exclusion; since several of the secondary efficacy analyses involve pooling of data from the FIX-HF-5C and original FIX-HF-5 studies, these details are provided for both populations.

Table 19: Subjects excluded from per-protocol population

Study	Subject	Group	Reason for Exclusion
FIX-HF-5C	06-404 RCW	OPTIMIZER	no device, not implanted
	08-407 MAJ	OPTIMIZER	no device, not implanted, WD prior to SSD
	51-423 M-W	OPTIMIZER	no device, not implanted
	51-454 MJP	OPTIMIZER	no device, not implanted
	57-409 GJD	OPTIMIZER	no device, LTF
	65-446 GDN	OPTIMIZER	no device, died prior to SSD
FIX-HF-5	08-212 J-G	OPTIMIZER	no device, died prior to SSD
	13-204STD	Control	WD prior to SSD

Study	Subject	Group	Reason for Exclusion
	13-206 WSD	OPTIMIZER	no device, WD prior to SSD
	13-212 JWG	Control	No follow-up, NYHA II, Not willing, cognitive impairment
	13-215 PJV	Control	WD prior to SSD
	17-221 JAW	Control	WD due to Control Group prior to follow-up
	20-227 LRM	OPTIMIZER	no device
	25-206 J-P	Control	no follow-up, HF meds not stable
	27-217 JBG	OPTIMIZER	no device, died prior to SSD
	28-203 B-C	OPTIMIZER	no device
	29-204 M-V	OPTIMIZER	no device, WD prior to SSD
	36-204 BTB	OPTIMIZER	no device
	36-206 RKG	OPTIMIZER	no device, WD prior to SSD

Complete case analyses are conducted for all secondary and supportive analyses. That is, all available data is used without imputation. Analyses are conducted for complete cases and for complete cases in the per protocol population.

1.4.6.4 Baseline Demographics

Tables 20 (continuous variables) and 21 (categorical variables) present comparisons of baseline variables between the Control and OPTIMIZER groups of the FIX-HF-5C study. There are no statistically significant differences between the groups in any of the variables, thus demonstrating that randomization of subjects produced balanced groups with respect to baseline characteristics.

Table 20: Baseline Demographics - Continuous Variables

Variable	OPTIMIZER Mean (SD) N Med (Min, Max)	Control Mean (SD) N Med (Min, Max)	P-value
Age (yrs)	63.09 (10.89) 74 63.6 (38.0, 86.8)	62.79 (11.38) 86 62.4 (30.7, 89.2)	0.7109[1]
QRS Duration (ms)	102.50 (12.58) 74 100 (76, 128)	103.62 (12.10) 86 104 (80, 129)	0.5867[1]
PR Interval (ms)	183.37 (36.86) 74 180.0 (114, 288)	184.57 (43.93) 86 178.0 (28, 320)	0.9809[1]
Holter (PVCs/24hr)	1599.5 (2009.0) 74 668 (0, 7370)	1176.8 (1712.4) 86 277.5 (0, 8514)	0.4334[1]
LVEF (%) (Core Lab)	33.08 (5.55) 74 32 (25, 45)	32.55 (5.18) 86 32 (25, 45)	0.5747[1]
LVEDD (mm) (Core Lab)	58.47 (7.17) 74 59 (40, 75)	60.20 (7.01) 82 59 (44, 77)	0.1984[1]
MLWHFQ	56.42 (22.95) 74 60.5 (1, 96)	57.35 (23.36) 86 60 (5, 99)	0.7365[1]
6MW (meters)	316.85 (88.37) 74	324.07 (89.71) 86	0.8724[1]

Variable	OPTIMIZER Mean (SD) N Med (Min, Max)	Control Mean (SD) N Med (Min, Max)	P-value
	308 (75, 462)	315 (120, 579)	
CPX (Core Lab)			
Peak VO_2 (ml/kg/min)	15.49 (2.61) 73[3] 15.70 (9.75, 19.70)	15.36 (2.82) 86 15.85 (9.10, 19.90)	0.8011[1]
Peak RER	1.15 (0.064) 73[3] 1.140 (1.015, 1315)	1.14 (0.074) 86 1.125 (0.975, 1.480)	0.4469[1]
Exercise Time (minutes)	11.38 (3.08) 73[3] 11.800 (3.208, 18.500)	10.58 (3.09) 86 11.163 (3.133, 18.033)	0.1286[1]
Physical Exam			
Weight (kg)	99.60 (20.72) 74 98.0 (52.7, 167.8)	100.33 (23.32) 86 96.8 (49.0, 155.1)	0.8442[1]
Height (cm)	174.77 (9.58) 74 175.0 (150.0 208.0)	174.40 (8.97) 86 175.0 (142.0, 201.0)	0.9019[1]
BMI (kg/m2)	32.49 (5.63) 74 32.0 (20.6, 46.6)	32.90 (6.90) 86 32.2 (19.1, 50.0)	0.7728[1]
Resting HR (bpm)	74.42 (11.35) 74 73.0 (54.0, 112.0)	76.45 (14.84) 86 76.5 (45.0, 137.0)	0.3281[2]
SBP (mmHg)	122.66 (17.66) 74 124 (88, 165)	126.04 (18.83) 86 122.(91, 196)	0.4870[1]
DBP (mmHg)	74.42 (11.35) 74 72.5 (54.0, 112.0)	76.45 (14.84) 86 76.5 (45.0, 137.0)	0.7427[1]

Program: Baseline.sas

1 Two-sided Wilcoxon rank sum test.
2 Two-sided unequal variance two-sample t-test.
3 One subject in the OPTIMIZER group did not have valid readings for the CPX testing.

Baseline parameters illustrate that subjects included in the FIX-HF-5C study met intended inclusion criteria and are generally representative of the US heart failure population with moderately severe heart failure (i.e., 25≤EF≤45). The typical subject in the study was in their early 60's with a narrow QRS duration and LVEF within the 25-45% inclusion criteria range. Peak VO_2 on CPX testing in the randomized group of subjects was approximately 15 ml/kg/min which is moderately reduced compared to the normal population. With BMI of approximately 32 kg/m^2, subjects were moderately obese but demonstrated mostly normotensive blood pressures at baseline

Table 21: Baseline Demographics and Medical History Categorical Variables

Variable	OPTIMIZER n/N (%)	Control n/N (%)	P-value
Male	54/74 (73.0)	68/86 (79.1)	0.4565[1]
Ethnicity			
White	55/74 (74.3)	61/86 (70.9)	0.9244[2]
Black	14/74 (18.9)	15/86 (17.4)	
Hispanic	0/74 (0.0)	1/86 (1.2)	

Variable	OPTIMIZER n/N (%)	Control n/N (%)	P-value
Native American	1/74 (1.4)	2/86 (2.3)	
Other	4/74 (5.4)	7/86 (8.1)	
CHF Etiology			
Ischemic	46/74 (62.2)	51/86 (59.3)	0.8497[2]
Idiopathic	22/74 (29.7)	29/86 (33.7)	
Other	6/74 (8.1)	6/86 (7.0)	
Prior MI	36/74 (48.6)	51/86 (59.3)	0.2043[1]
Prior CABG	18/74 (24.3)	23/86 (26.7)	0.8561[1]
Prior PTCA	36/74 (48.6)	43/86 (50.0)	0.8754[1]
ICD/PM System	65/74 (87.8)	73/86 (84.9)	0.6502[1]
Angina	5/74 (6.8)	6/86 (7.0)	1.0000[1]
Diabetes	38/74 (51.4)	42/86 (48.8)	0.8741[1]
History of Atrial Arrhythmias	25/74 (66.2)	35/86 (59.3)	0.4147[1]
Atrial Flutter	8/74 (10.8)	6/86 (7.0)	0.4154[1]
Atrial Fibrillation	20/74 (27.0)	27/86 (31.4)	0.6035[1]
Frequent PACs	3/74 (4.1)	1/86 (1.2)	0.3365[1]
Other Atrial Abnormalities	2/74 (2.7)	3/86 (3.5)	1.0000[1]
History of Ventricular Arrhythmias	26/74 (35.1)	28/86 (32.6)	0.7406[1]
Ventricle Fibrillation	5/74 (6.8)	8/86 (9.3)	0.7729[1]
Ventricular Tachycardia	19/74 (25.7)	19/86 (22.1)	0.7098
Frequent PVCs	8/74 (10.8)	7/86 (8.1)	0.5967[1]
NYHA (site)			
Class III	64/74 (86.5)	78/86 (90.7)	0.4575[1]
Class IV	10/74 (13.5)	8/86 (9.3)	

Program: Baseline.sas

1 Two-sided Fisher's exact test.
2 Two-sided Fisher-Freeman-Halton test.

The majority of subjects enrolled in the FIX-HF-5C study were white males, which is typical of a large recent heart failure study (e.g., the PARADIGM study.)[17]

The etiology of heart disease was ischemic in ~60% of the subjects. This finding is also consistent with a recent study of heart failure (e.g., the PARADIGM study.)[17] The history of atrial arrhythmias presented in the Table 21 represents remote history because subjects with recent persistent or permanent atrial fibrillation or atrial flutter were excluded from the study. The presence of ventricular arrhythmias as shown here is common for patients with predominantly ischemic heart failure. Approximately 90% of the randomized subjects in FIX-HF-5C were NYHA Class III at baseline assessment consistent with the target patient population.

1.4.6.5 Baseline Medications

Table 22 provides a comparison of baseline medications between the Control and

OPTIMIZER groups of the study. There were no statistically significant differences between the groups for any category of cardiovascular medication evaluated, so the groups were again shown to be well balanced after randomization. In both groups, approximately 83% of subjects were on ACE-I or ARB medications while over 95% of subjects in both groups were receiving beta blocker medication at baseline. Seventy-five percent of subjects were taking diuretics and approximately 35% of subjects were on an aldosterone inhibitor. The rate of diuretic therapy in FIX-HF-5C is similar to the rate reported in the PARADIGM study[17] which was ~80%.

Table 22: Baseline Medication

Medication	OPTIMIZER n/N (%)	Control n/N (%)	P-Value[1]
ACEi or ARB	61/74 (82.4)	72/86 (83.7)	0.8358
Angiotensin converting enzyme inhibitor (ACEi)	40/74 (54.1)	49/86 (57.0)	0.7511
Angiotensin receptor blocker (ARB)	21/74 (28.4)	25/86 (29.1)	1.0000
Beta Blocker	72/74 (97.3)	82/86 (95.3)	0.6870
Diuretic	56/74 (75.7)	68/86 (79.1)	0.7049
Second Diuretic[2]	5/74 (6.8)	8/86 (9.3)	0.7729
Ivabradine	2/74 (2.7)	4/86 (4.7)	0.6870
Digoxin	10/74 (13.5)	8/86 (9.3)	0.4575
Aldosterone Inhibitor	25/74 (33.8)	32/86 (37.2)	0.7410
Hydralazine	4/74 (5.4)	10/86 (11.6)	0.2615
Nitrates	18/74 (24.3)	26/86 (30.2)	0.4786
Entresto	2/74 (2.7)	3/86 (3.5)	1.0000
Calcium Channel Blocker	9/74 (12.2)	8/86 (9.3)	0.6132
Anti-arrhythmic	13/74 (17.6)	12/86 (14.0)	0.6630
Aspirin	54/74 (73.0)	59/86 (68.6)	0.6035
Coumadin	7/74 (9.5)	5/86 (5.8)	0.5490
Clopidogrel	15/74 (20.3)	25/86 (29.1)	0.2719

Program: Baseline.sas

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

1.4.6.6 Lead Type

Three lead types were employed in the study: St. Jude Medical, Biotronik, and Boston Scientific/Guidant. The frequency of use is shown in the Table 23.

Table 23: Number of Subjects with leads used in the study

Type of Lead	St. Jude Medical N	Biotronik N	BSC/Guidant N
Number of Subjects with each type of lead	37	20	11

1.4.6.7 Site Comparability Analyses

Comprehensive statistical analyses were conducted to demonstrate the

comparability of sites enrolling subjects in the study and to identify any differences between OUS and US sites that enrolled subjects. These detailed analyses are provided in their entirety in Attachment 03, the Statistical Analysis Report of Impulse Dynamics FIX-HF-5C Study. The formation of pseudo-sites by combining sites with low numbers of patients is outlined in Table 24 below.

Table 24: Pseudo-site Formation from Original Study Sites

Pseudo Site Number	Originals Site Number(s)	Number of Control Subjects	Number of Optimizer Subjects	Total Subjects
1	6, 8, 9, 15, 21, 32, 32, 36, and 88	16	10	26
2	41, 54, 55, 56, 57, 59, 69, and 89	14	11	25
3	51	15	13	28
4	65	13	12	25
5	70, 71, 72, 74, 75, 76, 78, and 79	12	12	24
6	90	16	16	32
	Total	**86**	**74**	**160**

Program: Create Patient Data.sas

The following two tables provide summaries of the significant differences found between pseudo-sites.

Table 25: Summary of Study Pseudo-Site Comparability[1] for Baseline Quantitative Endpoints

Variable	P-value for Study Pseudo-Site[2]
Age (yrs)	0.1015
QRS Duration (ms)	0.0937
PR Interval (ms)	0.6832
Holter (PVCs/24hr)	**0.0184**
LVEF (%) (Core Lab)	0.5187
LVEDD (mm) (Core Lab)	0.3244
MLWHFQ	**0.0004**
6MW (meters)	**<0.0001**
CPX (Core Lab)	
Peak VO_2 (ml/kg/min)	0.8917
RER	**0.0082**
Exercise Time (minutes)	0.0790
Weight (kg)	0.2585
Height (cm)	0.2424
BMI (kg/m2)	0.4117
HR (bpm)	**0.0016**
SBP (mmHg)	**0.0046**
DBP (mmHg)	**0.0316**

Program: By Site Analyses.sas

1 Analysis by general linear model analysis of variance with Type III sums of squares.
2 Pseudo-sites were used in this analysis and are defined in Table 21
p-value-2 sided

Subjects at Pseudo-site 3 (Study Site 51) appear to have a higher mean baseline Holter PVC than the subjects at the other pseudo-sites. Similarly, it appears that subjects at Pseudo-site 3 (Study Site 51) have a higher mean baseline score for the MLWHFQ than subjects at the other pseudo-sites. Subjects at Pseudo-site 5 (combined sites 70-79) appear to have a lower mean baseline Peak RER than subjects at the other pseudo-sites.

Pseudo-site 6 (Study Site 90) appears to have a higher mean baseline heart rate than the subjects at the other pseudo-sites. Similarly, subjects at Pseudo-site 6 (study Site 90) have a higher mean systolic blood pressure than subjects at the other pseudo-sites. Subjects at Pseudo-sites 1, 2, and 6 appear to have a higher mean baseline diastolic blood pressure than subjects at the other three pseudo-sites.

Table 26: Summary of Study Pseudo-Site by Baseline Categorical Endpoints

	Pseudo-Site						
	1	**2**	**3**	**4**	**5**	**6**	**P-value[1]**
Females	12/26 (46.2)	7/25 (28.0)	0/28 (0.0)	7/25 (28.0)	9/24 (37.5)	3/32 (9.4)	<0.0001
Males	14/26 (53.8)	18/25 (72.0)	28/28 (100.0)	18/25 (72.0)	15/24 (62.5)	29/32 (90.6)	
White	16/26 (61.54)	22/25 (88.00)	15/28 (53.57)	23/25 (92.00)	22/24 (91.67)	18/32 (56.25)	0.0002
Non-white	10/26 (38.46)	3/25 (12.00)	13/28 (46.43)	2/25 (8.00)	2/24 (8.33)	14/32 (43.75)	
Ischemic	14/26 (53.85)	17/25 (68.00)	21/28 (75.00)	16/25 (64.00)	17/24 (70.83)	12/32 (37.50)	0.0415
Non-Ischemic	12/26 (46.15)	8/25 (32.00)	7/28 (25.00)	9/25 (36.00)	7/24 (29.17)	20/32 (62.50)	
No History of PTCA	14/26 (53.85)	17/25 (68.00)	9/28 (32.14)	9/25 36.00)	10/24 (41.67)	22/32 (68.75)	0.0152
History of PTCA	12/26 (46.15)	8/25 (32.00)	19/28 (67.86)	16/25 (64.00)	14/24 (58.33)	10/32 (31.25)	
No History of Other Atrial	26/26 (100.00)	25/25 (100.00)	27/28 (96.43)	21/25 (84.00)	24/24 (100.00)	32/32 (100.00)	0.0056
History of Other Atrial	0/26 (0.00)	0/25 (0.00)	1/28 (3.57)	4/25 (16.00)	0/24 (0.00)	0/32 (0.00)	
No History of VA	9/26 (34.62)	10/25 (40.00)	10/28 (35.71)	16/25 (64.00)	3/24 (12.50)	6/32 (18.75)	0.0021
History of VA	17/26 (65.38)	15/25 (60.00)	18/28 (64.29)	9/25 (36.00)	21/24 (87.50)	26/32 (81.25)	
No History of VT	20/26 (76.92)	16/25 (64.00)	22/28 (78.57)	13/25 (52.00)	23/24 (95.83)	28/32 (87.50)	0.0031

	Pseudo-Site						
	1	2	3	4	5	6	P-value[1]
History of VT	6/26 (33.08)	9/25 (36.00)	6/28 (21.43)	12/25 (48.00)	1/24 (4.17)	4/32 (12.50)	
NYHA 3	24/26 (92.31)	24/25 (96.00)	22/28 (78.57)	25/25 (100.00)	24/24 (100.00)	23/32 (71.88)	0.0008
NYHA 4	2/26 (7.69)	1/25 (4.00)	6/28 (21.43)	0/25 (0.00)	0/24 (0.00)	9/32 (28.13)	

Program: By Site Analyses.sas

[1] Analysis by two-sided Fisher-Freeman-Halton test.

Note the following:

- There were no female subjects at Pseudo-site 3 whereas all of the other pseudo-sites had female subjects.
- Pseudo-sites 1, 3, and 6 had a higher percentage of non-white subjects than the remaining pseudo-sites.
- There was a much higher percentage of subjects with non-ischemic etiology at Pseudo-site 6 than at the other pseudo-sites.
- Subjects at Pseudo-sites 3, 4, and 5 have a higher percentage of subjects with prior PTCA than the other pseudo-sites.
- Subjects at Pseudo-sites 3 and 4 have subjects with some history of atrial abnormalities but the other four pseudo-sites have none.
- Subjects at Pseudo-site 4 have a much lower rate of ventricular arrhythmias than the subjects at the other pseudo-sites.
- Subjects at Pseudo-site 5 have a much lower rate of ventricular tachycardia than the subjects at the other pseudo-sites.
- Pseudo-sites 3 and 6 have a higher percentage of subjects in NYHA class 4 than the other pseudo-sites.

Table 27: Summary of Study Pseudo-Site by Baseline Medication Use

	Pseudo-Site						
	1	2	3	4	5	6	P-value (2-sided)
No ACEi Use	7/26 (26.92)	9/25 (36.00)	10/28 (35.71)	18/25 (72.00)	9/24 (37.50)	18/32 (56.25)	0.0117
ACEi Use	19/26 (73.08)	16/25 (64.00)	18/28 (64.29)	7/25 (28.00)	15/24 (62.50)	14/32 (43.75)	
No Diuretic Use	5/26 (19.23)	6/25 (24.00)	3/28 (10.71)	7/25 (28.00)	1/24 (4.17)	14/32 (43.75)	0.0072
Diuretic Use	21/26 (80.77)	19/25 (76.00)	25/28 (89.29)	18/25 (72.00)	23/24 (95.83)	18/32 (56.25)	
No Ivabradine Use	25/26 (96.15)	25/25 (100.00)	28/28 (100.00)	24/25 (96.00)	20/24 (83.33)	32/32 (100.00)	0.0111

	Pseudo-Site						
	1	**2**	**3**	**4**	**5**	**6**	**P-value (2-sided)**
Ivabradine Use	1/26 (3.85)	0/25 (0.00)	0/28 (0.00)	1/25 (4.00)	4/24 (16.67)	0/32 (0.00)	
No Digoxin Use	21/26 (80.77)	23/25 (92.00)	28/28 (100.00)	18/25 (72.00)	23/24 (95.83)	29/32 90.63)	0.0141
Digoxin Use	5/26 (19.23)	2/25 (8.00)	0/28 (0.00)	7/25 (28.00)	1/24 (4.17)	3/32 (9.38)	
No Aldosterone Inhibitor Use	14/26 (53.85)	20/25 (80.00)	19/28 (67.86)	16/25 (64.00)	5/24 (20.83)	29/32 (90.63)	<0.0001
Aldosterone Inhibitor Use	12/26 (46.15)	5/25 (20.00)	9/28 (32.14)	9/25 (36.00)	19/24 (79.17)	3/32 (9.38)	
No Hydralazine Use	20/26 (76.92)	23/25 (92.00)	24/28 (85.71)	24/25 96.00)	24/24 (100.00)	31/32 (96.88)	0.0369
Hydralazine Use	6/26 (23.08)	2/25 (8.00)	4/28 (14.29)	1/25 (4.00)	0/24 (0.00)	1/32 (3.12)	
No Nitrates Use	10/26 (38.46)	19/25 (76.00)	20/28 (71.43)	16/25 (64.00)	23/24 (95.83)	28/32 (87.50)	<0.0001
Nitrates Use	16/26 (61.54)	6/25 (24.00)	8/28 (28.57)	9/25 (36.00)	1/24 (4.17)	4/32 (12.50)	

Program: By Site Analyses.sas

Note the following:

- Subjects at Pseudo-sites 4 and 6 have a lower percentage using ace inhibitors than the subjects at the other pseudo-sites.
- Subjects at Pseudo-sites 4 and 6 have a lower percentage using diuretics than the subjects at the other pseudo-sites.
- Pseudo-sites 2, 3, and 6 have no subjects using Ivabradine but the other pseudo-sites have at least one subject with baseline Ivabradine use.
- Subjects at Pseudo-sites 1 and 4 have higher rates of digoxin use than subjects at the other pseudo-sites.
- Subjects at Pseudo-site 5 have a much higher rate of Aldosterone inhibitor use than subjects at the other pseudo sites.
- Subjects at Pseudo-sites 1 and 3 have a higher use of Hydralazine that subjects at the other pseudo-sites.
- Subjects at Pseudo-sites 5 and 6 have a much lower baseline rate of nitrate use than subjects at the other pseudo-sites.

Thus, as anticipated in a study with a relatively small sample size, several differences between pseudo sites emerge. Accordingly, for purposes of poolability, it is appropriate to assess if treatment effects differ among pseudo sites as will be detailed in the next section.

1.4.6.8 Analysis of Poolability of Data

To determine if the data can be pooled in estimation of the primary effectiveness endpoint, two analyses were conducted below per the SAP: one for the presence of a pseudo-site by treatment interaction and one for the presence of a geographic region by pseudo-site interaction. Additional exploration of the heterogeneity of the treatment effect by site and region can be found in the Primary & Key Secondary Analyses Report (Attachment 07).

1.4.6.8.1 Analysis of Poolability by Pseudo-site

The evaluation of a pseudo-site by treatment interaction was evaluated using the primary effectiveness mixed model specification adding pseudo-site as a random component along with the interaction of pseudo-site by treatment group. If the interaction of pseudo-site by treatment group has a P-value <0.15, the data were considered not poolable and required a model that includes pseudo-site as a random component.

The results of the pseudo-site poolability model are presented in the table below.

Table 28: Repeated Measures Analysis of Variance Pooling Analysis of Pseudo-Site

Effect	Numerator Degrees of Freedom	Denominator Degrees of Freedom	F-value	P-value[1]
Interaction Treatment Group by Pseudo-Site	6	279	0.43	0.8576

Program: By Site Analyses.sas

[1]The P-value is a two-sided Type III F-test from mixed model procedure.

Because the P-value for the interaction is greater than 0.15, the data can be pooled by site.

1.4.6.8.2 Analysis of Poolability by Geographic Region

The results of the geographic region poolability model are presented in the table below.

Table 29: Repeated Measures Analysis of Variance Pooling Analysis of Geographic Region

Effect	Numerator Degrees of Freedom	Denominator Degrees of Freedom	F-value	P-value[1]
Interaction Treatment Group by Region	2	279	0.25	0.7771

Program: By Site Analyses.sas

[1] The P-value is a two-sided Type III F-test from mixed model procedure.

Because the P-value for the interaction is greater than 0.15, from the perspective of geographic region, the data can be pooled.

1.4.6.9 Analysis of Medication Dose Changes

Information on both baseline and 24-week medications and doses were available from 152 patients among the FIX-HF-5C population, 81 in the Control group and 71 in the ACTIVE group. For each class of drug (ACE-inhibitors, ARBs, β-blockers, diuretics, second diuretic, or aldosterone inhibitor), we determined the total number of patients in each group in which the drug was changed, in addition to the number in which doses were increased and the number in which doses were decreased. Finally, the percentage of patients with increases and decreases in each drug class was determined and compared statistically (Fisher's Exact Test). As detailed in the tables below, there were no significant differences between groups in the percentage of patients with increases or decreases in any category.

Table 30: Summary of Medication dose changes

ACE-Inhibitor	Control	Active	P-value
Total Number with Change	17	13	
Number with Increase	8	8	
Number with Decrease	9	5	
% with Increase	9.9%	11.3%	0.7974
% with Decrease	11.1%	7.0%	0.4167
ARB	**Control**	**Active**	**P-value**
Total Number with Change	9	8	
Number with Increase	2	4	
Number with Decrease	7	4	
% with Increase	2.5%	5.6%	0.5438
% with Decrease	8.6%	5.6%	0.4187
β-Blocker	**Control**	**Active**	**P-value**
Total Number with Change	28	22	
Number with Increase	18	12	
Number with Decrease	10	10	
% with Increase	22.2%	16.9%	0.7299
% with Decrease	12.3%	14.1%	0.5406
Diuretic	**Control**	**Active**	**P-value**
Total Number with Change	14	18	
Number with Increase	8	11	
Number with Decrease	6	7	
% with Increase	9.9%	15.5%	0.3331
% with Decrease	7.4%	9.9%	0.7726
Second Diuretic	**Control**	**Active**	**P-value**
Total Number with Change	10	6	
Number with Increase	6	5	
Number with Decrease	4	1	
% with Increase	7.4%	7.0%	1.000
% with Decrease	4.9%	1.4%	0.3722
Aldosterone Inhibitor	**Control**	**Active**	**P-value**
Total Number with Change	7	4	
Number with Increase	4	3	
Number with Decrease	3	1	
% with Increase	4.9%	4.2%	1.000
% with Decrease	3.7%	1.4%	0.6233

P-value is two-sided from Fisher's Exact Test.

1.4.6.10 Primary Effectiveness Result

160 patients contributed 442 peak VO_2 observations across baseline, 12-week and 24-week follow-up visits. Imputation was performed such that if the reason for missing peak VO_2 values was death, zeroes were imputed for the missing values. If the reason for missing values was heart failure hospitalization, the missing peak VO_2 values were imputed as the minimum value from the cohort. There were no cases missing for heart failure hospitalization in the data set.

The following is a list of all 160 FIX-HF-5C subjects on order of Peak VO_2 from greatest positive change to greatest negative change.

Table 31a: Summary of the peak VO_2 values for the FIX-HF-5C study (Control Group)

				Complete Case			0's Imputed for Deaths		
Sr. no	Patient ID	Treatment Group	Baseline	12 Weeks	24 Weeks	Change from Baseline to 24 Weeks	12 Weeks	24 Weeks	Change from Baseline to 24 Weeks
1	65-413 J-R	CONTROL	10.5	15.3	15.4	4.9	15.3	15.4	4.9
2	65-470 JTH	CONTROL	16.9	20.3	21.05	4.15	20.3	21.05	4.15
3	51-419 DJG	CONTROL	14.1	14.95	18.25	4.15	14.95	18.25	4.15
4	06-406 MJP	CONTROL	16	17	19.7	3.7	17	19.7	3.7
5	51-452 KCH	CONTROL	19.1	20.5	22.65	3.55	20.5	22.65	3.55
6	71-406 AAA	CONTROL	18.65	21.55	21.9	3.25	21.55	21.9	3.25
7	65-431 KET	CONTROL	15.55	Not Done	18.55	3	Not Done	18.55	3
8	09-407 GMW	CONTROL	16.85	19	19.6	2.75	19	19.6	2.75
9	65-429 EDC	CONTROL	15.35	17.85	18.1	2.75	17.85	18.1	2.75
10	57-408 DDM	CONTROL	16.15	17.3	18.7	2.55	17.3	18.7	2.55
11	59-408 FJS	CONTROL	19.9	21.9	22.05	2.15	21.9	22.05	2.15
12	65-480 SLR	CONTROL	12.05	13	14.15	2.1	13	14.15	2.1
13	09-408 DPM	CONTROL	12.1	13.5	14.1	2	13.5	14.1	2
14	51-455 E-B	CONTROL	12.9	14.15	14.45	1.55	14.15	14.45	1.55
15	70-426 K-S	CONTROL	16.1	16.45	17.5	1.4	16.45	17.5	1.4
16	65-402 JAD	CONTROL	18.8	Inadequate	19.9	1.1	Inadequate	19.9	1.1
17	55-413 SLS	CONTROL	12.2	12.35	13.2	1	12.35	13.2	1
18	08-405 BLB	CONTROL	12.5	13.7	13.3	0.8	13.7	13.3	0.8
19	51-427 ABG	CONTROL	19.5	20.3	20.2	0.7	20.3	20.2	0.7
20	55-408 WSG	CONTROL	13	Not Done	13.6	0.6	Not Done	13.6	0.6
21	65-450 VGH	CONTROL	18.65	15	19.1	0.45	15	19.1	0.45

				Complete Case			0's Imputed for Deaths		
Sr. no	Patient ID	Treatment Group	Baseline	12 Weeks	24 Weeks	Change from Baseline to 24 Weeks	12 Weeks	24 Weeks	Change from Baseline to 24 Weeks
22	32-408 WJJ	CONTROL	15	17.35	15.45	0.45	17.35	15.45	0.45
23	75-409 CCC	CONTROL	12.8	14.35	13	0.2	14.35	13	0.2
24	90-434 D-P	CONTROL	19.75	20.5	19.95	0.2	20.5	19.95	0.2
25	90-446 MJB	CONTROL	16.8	19.4	17	0.2	19.4	17	0.2
26	51-448 KAL	CONTROL	11.85	12.1	11.9	0.05	12.1	11.9	0.05
27	51-438 RKT	CONTROL	12.65	13	12.7	0.05	13	12.7	0.05
28	88-405 PAS	CONTROL	14.4	14.05	14.4	0	14.05	14.4	0
29	15-403 CAW	CONTROL	16.45	16.4	16.45	0	16.4	16.45	0
30	51-432 RAT	CONTROL	14.55	12.2	14.5	-0.05	12.2	14.5	-0.05
31	51-453 JRB	CONTROL	17.7	15.75	17.6	-0.1	15.75	17.6	-0.1
32	51-433 BSG	CONTROL	11.1	11.7	10.7	-0.4	11.7	10.7	-0.4
33	90-404 L-L	CONTROL	17.2	18.9	16.8	-0.4	18.9	16.8	-0.4
34	08-403 J-O	CONTROL	15.85	15.5	15.4	-0.45	15.5	15.4	-0.45
35	65-457 SAB	CONTROL	15.65	14	15.1	-0.55	14	15.1	-0.55
36	54-415 TPC	CONTROL	15.85	15.9	15.05	-0.8	15.9	15.05	-0.8
37	90-450 DAR	CONTROL	11.1	11.2	10.05	-1.05	11.2	10.05	-1.05
38	57-414 E-A	CONTROL	16.3	17.8	15.2	-1.1	17.8	15.2	-1.1
39	90-429 R-R	CONTROL	17.65	19.1	16.45	-1.2	19.1	16.45	-1.2
40	65-475 LPW	CONTROL	18.6	18.9	17.4	-1.2	18.9	17.4	-1.2
41	57-416 LAB	CONTROL	17.2	14.8	15.9	-1.3	14.8	15.9	-1.3
42	08-401 D-F	CONTROL	14.3	13.6	13	-1.3	13.6	13	-1.3
43	90-444 JSR	CONTROL	10.4	10.9	9.1	-1.3	10.9	9.1	-1.3
44	89-406 A-M	CONTROL	16.3	15.3	14.9	-1.4	15.3	14.9	-1.4

				Complete Case			0's Imputed for Deaths		
Sr. no	Patient ID	Treatment Group	Baseline	12 Weeks	24 Weeks	Change from Baseline to 24 Weeks	12 Weeks	24 Weeks	Change from Baseline to 24 Weeks
45	75-423 FFF	CONTROL	13.5	13.5	12.05	-1.45	13.5	12.05	-1.45
46	90-415 J-M	CONTROL	15.45	13.3	14	-1.45	13.3	14	-1.45
47	90-403 B-L	CONTROL	15.8	14.1	14.25	-1.55	14.1	14.25	-1.55
48	06-403 GAB	CONTROL	13.25	9.9	11.55	-1.7	9.9	11.55	-1.7
49	56-402 CES	CONTROL	10.5	11.2	8.8	-1.7	11.2	8.8	-1.7
50	76-404 DDD	CONTROL	18	17.7	16.3	-1.7	17.7	16.3	-1.7
51	75-430 KKK	CONTROL	18.05	19.3	16.3	-1.75	19.3	16.3	-1.75
52	41-401 RBF	CONTROL	13.05	12.75	11.15	-1.9	12.75	11.15	-1.9
53	36-404 EHT	CONTROL	18.4	17.8	16.45	-1.95	17.8	16.45	-1.95
54	89-411 JFB	CONTROL	18.4	17.75	16.25	-2.15	17.75	16.25	-2.15
55	06-410 SNJ	CONTROL	16.2	Not Done	13.8	-2.4	Not Done	13.8	-2.4
56	65-464 GLW	CONTROL	17.5	16.75	15.1	-2.4	16.75	15.1	-2.4
57	90-414 J-P	CONTROL	15.9	13.6	13.45	-2.45	13.6	13.45	-2.45
58	51-403 O-J	CONTROL	11.8	10.5	9.1	-2.7	10.5	9.1	-2.7
59	90-447 TLG	CONTROL	19.75	18.2	17.05	-2.7	18.2	17.05	-2.7
60	75-404 BBB	CONTROL	15.1	15.5	12.3	-2.8	15.5	12.3	-2.8
61	51-462 JPL	CONTROL	18.1	17	15.3	-2.8	17	15.3	-2.8
62	69-401 M-K	CONTROL	15.05	12.6	12.25	-2.8	12.6	12.25	-2.8
63	36-401 RLQ	CONTROL	19.15	16.9	16.25	-2.9	16.9	16.25	-2.9
64	51-457 CAR	CONTROL	17.55	15.5	14.2	-3.35	15.5	14.2	-3.35
65	51-418 C-R	CONTROL	19.1	14.45	15.35	-3.75	14.45	15.35	-3.75
66	51-461 RGB	CONTROL	17.1	14.8	13	-4.1	14.8	13	-4.1
67	90-435 L-S	CONTROL	13.1	8.5	8.95	-4.15	8.5	8.95	-4.15

				Complete Case			0's Imputed for Deaths		
Sr. no	Patient ID	Treatment Group	Baseline	12 Weeks	24 Weeks	Change from Baseline to 24 Weeks	12 Weeks	24 Weeks	Change from Baseline to 24 Weeks
68	90-407 A-S	CONTROL	17.4	14.1	13	-4.4	14.1	13	-4.4
69	54-409 DMD	CONTROL	15.65	10.95	11.05	-4.6	10.95	11.05	-4.6
70	90-423 M-C	CONTROL	17.5	11.4	10.65	-6.85	11.4	10.65	-6.85
71	21-402 A-C	CONTROL	14.3	14.05	Inadequate		14.05	Inadequate	
72	32-402 R-P	CONTROL	15.7	14.65	Not Done		14.65	Not Done	
73	41-405 ACW	CONTROL	9.1	Not Done	Not Done		Not Done	Not Done	
74	51-467 TDD	CONTROL	16.15	11.6	Not Done		11.6	Not Done	
75	65-421 DTJ	CONTROL	14.7	Not done	Not done		Not done	Not done	
76	65-422 RTH	CONTROL	17.8	Died	Died		0	0	-17.8
77	65-427 BAC	CONTROL	13.7	Died	Died		0	0	-13.7
78	70-411 M-K	CONTROL	17.7	Withdrawn	Withdrawn		Withdrawn	Withdrawn	
79	70-415 A-H	CONTROL	17.45	Inadequate	Inadequate		Inadequate	Inadequate	
80	71-401 XXX	CONTROL	18.05	Withdrawn	Withdrawn		Withdrawn	Withdrawn	
81	72-408 HHH	CONTROL	10.15	Inadequate	Death		Inadequate	0	-10.15
82	75-424 GGG	CONTROL	10.5	Inadequate	Not Done		Inadequate	Not Done	
83	88-407 WMR	CONTROL	10.2	Withdrawn	Withdrawn		Withdrawn	Withdrawn	
84	90-402 M-O	CONTROL	10.7	Death	Death		0	0	-10.7
85	90-408 G-M	CONTROL	17.85	Not Done	Not Done		Not Done	Not Done	
86	90-437 K-J	CONTROL	10.35	9.65	Not Done		9.65	Not Done	
Mean			**15.361**	**15.211**	**15.162**	**-0.504**	**14.586**	**14.343**	**-1.184**

Program: Primary Efficacy Endpoint Listing.sas

Table 31b: Summary of the peak VO_2 values for the FIX-HF-5C study (Optimizer Group)

				Complete Case			0's Imputed for Deaths		
Sr. no	Patient ID	Treatment Group	Baseline	12 Weeks	24 Weeks	Change from Baseline to 24 Weeks	12 Weeks	24 Weeks	Change from Baseline to 24 Weeks
1	51-411 J-B	ACTIVE	13.9	16.95	19.8	5.9	16.95	19.8	5.9
2	79-402 BBB	ACTIVE	14.75	20.7	20.4	5.65	20.7	20.4	5.65
3	90-424 H-F	ACTIVE	17.35	21.9	22.85	5.5	21.9	22.85	5.5
4	65-408 HDF	ACTIVE	17.85	20.3	22.3	4.45	20.3	22.3	4.45
5	06-409 DKW	ACTIVE	13.45	15.4	17.4	3.95	15.4	17.4	3.95
6	51-417 CWJ	ACTIVE	9.75	12.3	13.4	3.65	12.3	13.4	3.65
7	51-464 V-S	ACTIVE	19.6	23.25	23.2	3.6	23.25	23.2	3.6
8	51-435 KLA	ACTIVE	18.1	16.9	20.85	2.75	16.9	20.85	2.75
9	90-442 GSG	ACTIVE	16.95	18.45	19.65	2.7	18.45	19.65	2.7
10	78-401 AAA	ACTIVE	16.7	19.55	19.3	2.6	19.55	19.3	2.6
11	90-449 HES	ACTIVE	14.5	17.1	17	2.5	17.1	17	2.5
12	41-404 JJE	ACTIVE	17.55	18.45	19.9	2.35	18.45	19.9	2.35
13	65-409 DTA	ACTIVE	14.3	15.9	16.6	2.3	15.9	16.6	2.3
14	72-402 BBB	ACTIVE	18.4	19.05	20.6	2.2	19.05	20.6	2.2
15	54-404 JAS	ACTIVE	18.5	19.45	20.55	2.05	19.45	20.55	2.05
16	54-420 JFK	ACTIVE	15.75	17.3	17.65	1.9	17.3	17.65	1.9
17	51-454 MJP	ACTIVE	12.1	15.25	13.95	1.85	15.25	13.95	1.85
18	65-432 BRB	ACTIVE	18.55	20.8	20.15	1.6	20.8	20.15	1.6
19	75-402 AAA	ACTIVE	14.85	15.8	16.3	1.45	15.8	16.3	1.45

				Complete Case			0's Imputed for Deaths		
Sr. no	Patient ID	Treatment Group	Baseline	12 Weeks	24 Weeks	Change from Baseline to 24 Weeks	12 Weeks	24 Weeks	Change from Baseline to 24 Weeks
20	56-405 CFR	ACTIVE	11.15	12.7	12.45	1.3	12.7	12.45	1.3
21	65-403 STP	ACTIVE	13.15	12.2	14.4	1.25	12.2	14.4	1.25
22	75-420 EEE	ACTIVE	13.2	15.4	14.25	1.05	15.4	14.25	1.05
23	65-471 SLC	ACTIVE	16.35	15.7	17.4	1.05	15.7	17.4	1.05
24	90-406 H-R	ACTIVE	16.05	19.3	16.8	0.75	19.3	16.8	0.75
25	65-466 JWS	ACTIVE	17.9	15.7	18.6	0.7	15.7	18.6	0.7
26	90-413 G-G	ACTIVE	10.2	10.45	10.9	0.7	10.45	10.9	0.7
27	74-401 AAA	ACTIVE	15.95	16.5	16.65	0.7	16.5	16.65	0.7
28	75-427 HHH	ACTIVE	15.5	17	16.2	0.7	17	16.2	0.7
29	65-406 PAT	ACTIVE	15.45	13.25	15.85	0.4	13.25	15.85	0.4
30	51-446 JEW	ACTIVE	10.9	12.5	11.25	0.35	12.5	11.25	0.35
31	32-404 LMD	ACTIVE	16.9	13.7	17.2	0.3	13.7	17.2	0.3
32	09-402 JWA	ACTIVE	14.7	14.25	14.9	0.2	14.25	14.9	0.2
33	55-407 CRS	ACTIVE	13.4	14.3	13.6	0.2	14.3	13.6	0.2
34	51-444 JAF	ACTIVE	13.95	16.75	14.1	0.15	16.75	14.1	0.15
35	51-426 SLS	ACTIVE	10.2	9.25	10.3	0.1	9.25	10.3	0.1
36	21-404 D-C	ACTIVE	10.05	10.05	10.05	0	10.05	10.05	0
37	90-431 JCP	ACTIVE	13.6	14.4	13.6	0	14.4	13.6	0
38	51-423 M-W	ACTIVE	18.1	15.4	17.9	-0.2	15.4	17.9	-0.2
39	57-413 DEB	ACTIVE	16.3	16.7	15.95	-0.35	16.7	15.95	-0.35
40	51-456 WFC	ACTIVE	12.9	13.9	12.45	-0.45	13.9	12.45	-0.45

				Complete Case			0's Imputed for Deaths		
Sr. no	Patient ID	Treatment Group	Baseline	12 Weeks	24 Weeks	Change from Baseline to 24 Weeks	12 Weeks	24 Weeks	Change from Baseline to 24 Weeks
41	65-447 SLG	ACTIVE	18.15	17.9	17.6	-0.55	17.9	17.6	-0.55
42	65-460 RDB	ACTIVE	13.8	13.7	13.2	-0.6	13.7	13.2	-0.6
43	55-409 GLF	ACTIVE	15.7	16.65	15.05	-0.65	16.65	15.05	-0.65
44	65-445 GIC	ACTIVE	12.9	12.8	11.85	-1.05	12.8	11.85	-1.05
45	65-451 G-G	ACTIVE	14.75	12.45	13.35	-1.4	12.45	13.35	-1.4
46	75-435 PPP	ACTIVE	18.2	16.85	16.8	-1.4	16.85	16.8	-1.4
47	55-404 DBG	ACTIVE	18.3	18.4	16.8	-1.5	18.4	16.8	-1.5
48	90-405 M-R	ACTIVE	19.4	19.25	17.85	-1.55	19.25	17.85	-1.55
49	32-409 AMD	ACTIVE	16.9	18.1	15.3	-1.6	18.1	15.3	-1.6
50	89-402 DJB	ACTIVE	18.95	18.2	17.25	-1.7	18.2	17.25	-1.7
51	90-453 DSG	ACTIVE	17.65	17.5	15.9	-1.75	17.5	15.9	-1.75
52	06-402 PAS	ACTIVE	18.85	17.9	17.05	-1.8	17.9	17.05	-1.8
53	90-417 T-T	ACTIVE	14.2	13.35	12.25	-1.95	13.35	12.25	-1.95
54	90-411 RHJ	ACTIVE	12.85	12.75	10.6	-2.25	12.75	10.6	-2.25
55	51-459 CDS	ACTIVE	14.7	13.3	12.4	-2.3	13.3	12.4	-2.3
56	51-434 RLM	ACTIVE	18.4	19.7	15.75	-2.65	19.7	15.75	-2.65
57	75-416 DDD	ACTIVE	13.15	12.2	10.4	-2.75	12.2	10.4	-2.75
58	09-401 DLH	ACTIVE	11.9	10.35	8.9	-3	10.35	8.9	-3
59	90-451 CLC	ACTIVE	14.55	12.45	11.3	-3.25	12.45	11.3	-3.25
60	90-432 E-C	ACTIVE	17.9	16.75	13.95	-3.95	16.75	13.95	-3.95
61	90-422 G-W	ACTIVE	19.7	15.6	15.5	-4.2	15.6	15.5	-4.2

				Complete Case			0's Imputed for Deaths		
Sr. no	Patient ID	Treatment Group	Baseline	12 Weeks	24 Weeks	Change from Baseline to 24 Weeks	12 Weeks	24 Weeks	Change from Baseline to 24 Weeks
62	55-410 BGS	ACTIVE	16.3	8.95	11.75	-4.55	8.95	11.75	-4.55
63	90-420 D-G	ACTIVE	17.25	13.4	12.5	-4.75	13.4	12.5	-4.75
64	90-428 T-K	ACTIVE	15.65	10.45	10.2	-5.45	10.45	10.2	-5.45
65	51-420 KAS	ACTIVE	17.7	15.9	12	-5.7	15.9	12	-5.7
66	90-426 S-G	ACTIVE	17.3	12.75	10	-7.3	12.75	10	-7.3
67	06-404 RCW	ACTIVE	14	Not Done	Not Done		Not Done	Not Done	
68	08-407 MAJ	ACTIVE	18.15	Withdrawn	Withdrawn		Withdrawn	Withdrawn	
69	57-409 GJD	ACTIVE	16.45	LTF	LTF		LTF	LTF	
70	65-446 GDN	ACTIVE	10.85	Died	Died		0	0	-10.85
71	70-410 V-P	ACTIVE		Inadequate	Inadequate		Inadequate	Inadequate	
72	72-406 FFF	ACTIVE	15.2	Inadequate	Inadequate		Inadequate	Inadequate	
73	75-429 JJJ	ACTIVE	18.8	Not Done	Not Done		Not Done	Not Done	
74	88-402 SET	ACTIVE	13.35	12.45	Death		12.45	0	-13.35
Mean			**15.489**	**15.586**	**15.487**	**-0.027**	**15.357**	**15.032**	**-0.027**

Program: Primary Efficacy Endpoint Listing.sas

The primary effectiveness outcome measures by treatment group over time are summarized in Figure 15 and Table 32. The model-based estimated mean difference in peak VO_2 at 24 weeks between CCM™ Treatment and Control groups was 0.836 ml/kg/min (15.042 vs. 14.206 mlO_2/kg/min, respectively), with a 95% Bayesian credible interval of (0.123, 1.552 mlO_2/kg/min). The probability that CCM™ treatment is superior to Control is 0.989, which exceeds the 0.975 criteria required for statistical significance of the primary endpoint.

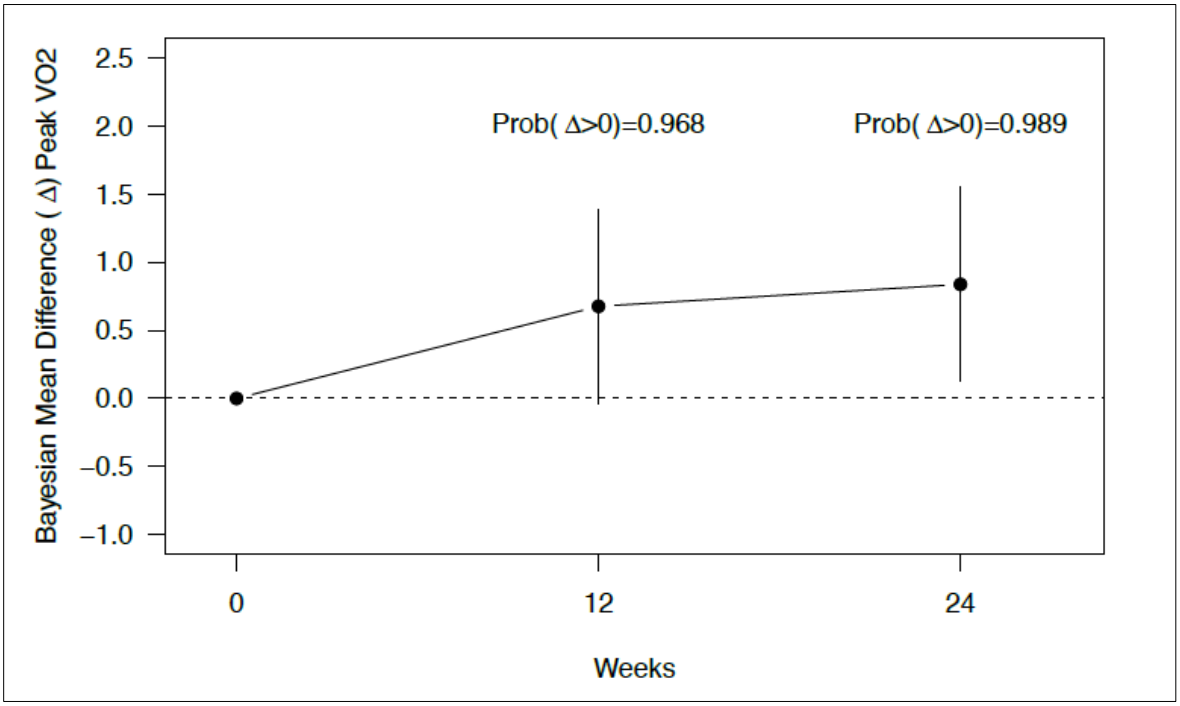


Figure 15: Bayesian Modeled Treatment Mean Difference (Δ) Peak VO_2 by Time*
***N's for each time point are shown in Table 32 below**

Table 32: "Bayesian Primary Analysis Results (with Borrowing)"

Borrowing (Bayes)					
Time	**TmtDiff**	**LL**	**UL**	**SE**	**P(Superior)**
12 Weeks	0.675	-0.037	1.387	0.363	0.968
24 Weeks	0.836	0.123	1.552	0.364	0.989

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

Summarizing the FIX-HF-5 and FIX-HF-5C studies separately (Figure 16), the model-based estimated treatment differences at 24 weeks in FIX-HF-5 and FIX-HF-5C studies are 1.080 mlO_2/kg/min (0.413, 1.759 mlO_2/kg/min) and 0.793 mlO_2/kg/min (-0.099, 1.684 mlO_2/kg/min), respectively. The primary analysis for FIX-HF-5C (with borrowing) appropriately leverages information from both studies to provide a more robust estimate of the treatment difference.

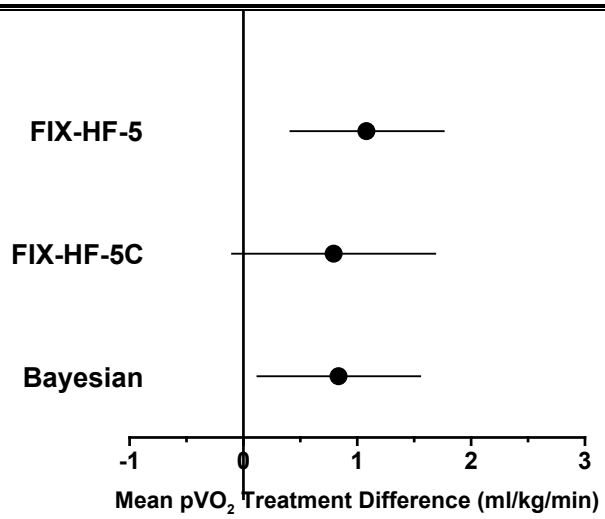


Figure 16: "24-Week Modeled Mean PVO2 Treatment Difference by Study"

For reference, the mean and SD of peak VO_2 observed in the FIX-HF-5C study alone by group and time are summarized in Table 33a and 33b below.

Table 33a: Number of Observations, Mean, SD of Peak VO_2 by Group and Time

	Nobs(observed)		Nobs(missing)		Mean		Standard Deviation	
	Control	Active	Control	Active	Control	Active	Control	Active
Baseline	86	73	0	1	15.36	15.49	2.81	2.61
12 Weeks	73	68	10	4	14.93	15.48	3.33	3.28
24 Weeks	74	68	6	4	14.79	15.28	3.54	3.66

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

Table 33b: Number of Observations, Mean, SD of Peak VO2 by Group and Time (FIX-HF-5)

	Nobs(observed)		Nobs(missing)		Mean		Standard Deviation	
	Control	Active	Control	Active	Control	Active	Control	Active
Baseline	112	117	1	0	14.95	14.60	2.83	2.95
12 Weeks	93	103	7	6	14.62	14.54	3.12	3.30
24 Weeks	89	99	8	9	14.21	14.99	3.02	3.48

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

Thus, the results of the analysis of the primary effectiveness endpoint of peak VO_2 demonstrate superiority of CCM treatment over Control in the primary endpoint. This allows us to conclude that the primary effectiveness endpoint has been met and that CCM™ therapy has successfully demonstrated effectiveness

in this study.

The following data confirm the adequacy of CPX tests employed in the determinations of peak VO_2 and RER.

Eighty-six (86) subjects were randomized to Control and 74 were randomized to OPTIMIZER. All have been accounted for in the table below, with regard to their 24-week CPX testing adequacy determinations. Seventy-two (72) Control subjects and 68 OPTIMIZER subjects performed the 24-week CPX testing. 77.8% of the Control subjects that performed the 24-week CPX testing had 2 adequate tests done and similarly, 77.9% of the OPTIMIZER subjects had 2 adequate tests. The subjects that had only one or zero adequate tests were generally not willing or able to perform a third test, and in some cases, they were unable to perform a second test as indicated in the table below. Only one of these subjects performed 2 inadequate tests, a third test was requested and performed, and that third test was deemed adequate.

Table 34: CPX test summary in Control and OPTIMIZER group

24 Week CPX Tests	CONTROL (86 subjects)	OPTIMIZER (74 subjects)
Both tests adequate	56 (65.1%)	53 (71.6%)
One test adequate	14 (16.3) - 2 of the 14 subjects only performed 1 test	13 (17.6%) - 1 of the 13 subjects only performed 1 test
Zero tests adequate	2 (2.3%) - 3rd test could not be done	2 (2.7%) - 3rd test could not be done
Third test	0	1 (included in the 13 above with 1 adequate test listed above)
No testing performed	14 (16.3%) • 4 deaths • 3 early withdrawal • 7 patients refused or unable	6 (8.1%) • 2 deaths • 1 LTF • 1 early withdrawal • 2 patients refused or unable

Discussion of pVO_2 results

The studies primary endpoint, a difference in peak VO_2 between groups, was met. This difference was arrived at by a reduction of peak VO_2 in the control group and a maintenance of peak VO_2 in the treatment group after 6-month follow-up. Thus, it can be concluded that in this study and included cohort, CCM prevented worsening of exercise tolerance. It is typically expected in such a clinical trial that exercise tolerance would be maintained in the Control group and would increase in the treatment group; for example, such expected findings have generally been identified in prior studies of cardiac resynchronization therapy

(CRT). It is therefore relevant to further discuss the current findings.

First, the purpose of a randomized trial is to be able to account for (i.e., balance) unanticipated confounding factors and behaviors between groups. Clinical trials and trial programs enroll unique populations based on unique eligibility criteria. In the FIX-HF-5 / FIX-HF-5C trials, we enrolled a group of patients who remained substantially symptomatic despite contemporary guideline-directed medical therapies. If left alone, these patients demonstrate disease progression as is evident by the progressive fall in peak VO_2. Observing this is part of the beauty of the randomized parallel-control trial design. As detailed further below, the consistency between FIX-HF-5 and FIX-HF-5C supports that this observation is population-based, real, and not methodological. Preventing disease progression is an acknowledged goal of heart failure therapy.

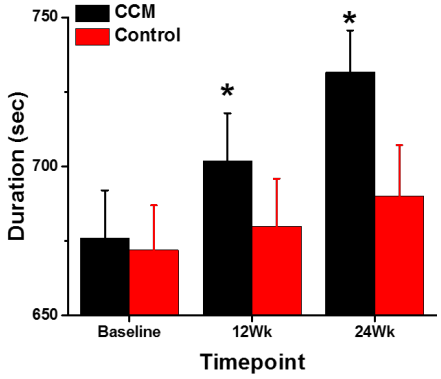
Second, it is important to note that, to the best of our knowledge, no prior study has invested as much time, effort and financial resources to ensure the quality of every cardiopulmonary stress test (CPX). Quality measures taken in the FIX-HF-5C study, included: quality assurance testing at every site to validate equipment every 6 months; sending technicians to perform tests upon requests of the sites or when the core lab identified issues with test performance; mandating two tests at each timepoint; and rapid centralized reads of test quality and asking for additional tests when quality metrics were not met. Similar measures were taken in the FIX-HF-5 study with the exception of two tests at each timepoint. Thus, we believe that the data of the current study are valid in that they reflect what can be expected from serial assessments of exercise tolerance in the target population.

To provide a perspective on the impact of the quality metrics, from among the 160 patients enrolled in FIX-HF-5C (86 Control patients; 74 CCM treated patients) ~880 CPX tests were conducted. Strict, prospectively defined criteria were applied by a blinded core lab to assess test "adequacy" and only "adequate" tests were included for analysis. It turned out that ~90% of tests were deemed adequate and included in the final analysis. We believe these methods further contribute importantly to the reliability of the CPX results obtained in FIX-HF-5C study.

Third, the finding of decreased peak VO_2 in the control group was very similar to what was observed in the original FIX-HF-5 study and now confirmed prospectively in the stand-alone data of the FIX-HF-5C study. This provides confidence in the robustness of the observation when studies are performed with the type of oversight detailed above.

Finally, regarding exercise physiology, it is important to consider the impact of treatment on exercise duration. In the pooled FIX-HF-5 and FIX-HF-5C dataset, peak VO_2 decreased but exercise duration was constant in the Control group (147 paired observations, 11.2 vs 11.5 min, p=0.84). In contrast, in the CCM treatment

group, peak VO_2 was relatively constant, but exercise duration increased significantly by almost 1 min (11.3 vs 12.2 min, 159 paired observations, $p<0.001$). Please refer to the following Figure and Table (data pooled from FIX-HF-5 and FIX-HF-5C; error bars are SEMs) for further details. Thus, we identify another difference between the groups. Importantly, since values of RER are constant across time, this does not appear to be a result of differences in patient effort between groups.



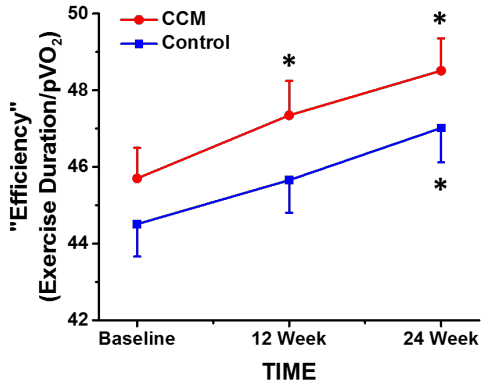
Exercise Duration (seconds) by Group and Time

	CCM	SD	Control	SD
Baseline	676	179	672	203
12 Week	702	202	680	210
24 Week	732	206	690	212

Exercise Duration (mins) by Group and Time

	CCM	SD	Control	SD
Baseline	11.3	3.0	11.2	3.4
12 Week	11.7	3.4	11.3	3.5
24 Week	12.2	3.4	11.5	3.5

Considering that a continuous treadmill ramp protocol was used in the conduct of the exercise tests, exercise time is directly related to workload. Therefore, the ratio of exercise time (a surrogate of work performed) to peak VO_2 (energy utilization) can be considered as an index of overall metabolic efficiency. Improved metabolic efficiency is commonly expected on repeat exercise testing due to habituation (i.e., patient familiarity with the test) and possibly some degree of physical conditioning. Interestingly, this efficiency ratio increased from baseline to 6 months by similar amounts in both groups: 44.5 vs 47.0 [sec/(mlO2/min), p=0.001] in controls compared to 45.7 vs 48.5 [sec/(mlO2/min), p=0.007] in CCM treatment (p=ns between groups). These findings are summarized in the next Figure. As noted above, this is also in the context of no change of RER values between baseline and 6-months such that changes in patient effort are considered to be accounted for.



*p<0.05 vs respective baseline value
No difference in changes between groups
Error bars show SEMs

Since CPX tests were done using a continuous speed ramp test, exercise duration is proportional to workload. Therefore, an index of metabolic efficiency is provided by the ratio between exercise duration and peak VO2.

Efficiency (seconds/pVO2) by Group and Time

	CCM	SD	Control	SD
Baseline	45.7	10.6	44.5	11.7
12 Week	47.3	11.6	45.7	10.9
24 Week	48.5	10.6	47.0	10.9

The fact that this efficiency index improved as expected, and comparably in both groups speaks to the equal treatment of study subjects in both groups and, we believe, also speaks to the blindness of the core lab interpretations.

Thus, patients in the CCM group were able to do more work than Controls (as evidenced by the significant increase in exercise duration. However, due to the apparent increase in metabolic efficiency in the context of a high degree of oversight during the conduct of the tests, increased work was able to be performed at the same peak VO_2.

In summary, the finding that peak VO_2 declined in controls in the FIX-HF-5C study is prospective confirmation of what was generally observed in our prior FIX-HF-5 study and speaks to the robustness of the observation.

The tests were performed with strict oversight by blinded core lab and "as needed" traveling exercise physiologist to ensure the highest possible test quality and inclusion only of "adequate" tests.

Although peak VO_2 stayed relatively constant, exercise duration (an index of total workload in our continuous ramp study) increased significantly in the treatment group. In Controls, duration stayed constant but peak VO_2 decreased. Apparent metabolic efficiency improved comparably in both groups. Overall, a significant treatment effect of CCM is demonstrated.

1.4.6.11 Sensitivity Analyses

The conclusion of CCM™ superiority with respect to mean peak VO_2 was consistent across all sensitivity analyses (detailed in Attachment 07 Primary & Key Secondary Analyses Report). These included various methods of imputation for missing data (missing data due to death imputed as 0, imputed as the lowest pVO_2 at any visit, or no imputation), as well as an assessment of site-to-site heterogeneity of the treatment effect. The conclusion of CCM™ superiority with respect to mean pVO_2 was consistent across all sensitivity analyses. In addition, it was noted that the primary analysis would achieve statistical significance with

any borrowing weight of 0.11 or larger (as noted above, 0.30 was pre-specified in the analysis plan).

In addition to the sensitivity analyses, there are two additional potential limitations of the Bayesian analysis:

a. The analysis of the FIX-HF-5 data used for borrowing in the Bayesian analysis included one patient with a baseline NYHA class II. The primary outcome (peak VO_2) was missing at 12 and 24 weeks for this patient, so impact of including this patient on the FIX-HF-5 analysis was minimal.

b. There was no imputation of missing data in the FIX-HF-5 analysis submitted to the FDA in the FIX-HF-5C simulations (i.e. all simulations used a "completed case" analysis of FIX-HF-5 for borrowing). However, a FIX-HF-5 "complete case" analysis (for borrowing) is inconsistent with the primary analysis of FIX-HF-5C, which imputes missing data due to death in FIX-HF-5C as 0's. There are a total of 6 patients in the FIX-HF-5 study who are missing peak VO_2 due to death, of which 5 are in the active treatment group and 1 is in the control group.

   Given these considerations, we repeated the FIX-HF-5C primary analysis with 30% borrowing of FIX- HF-5 data, in which the FIX-HF-5 analysis excludes the one patient with NYHA class II and imputes missing peak VO_2 data due to death as 0's for the above 6 patients. This involves fitting a Bayesian model on the FIX-HF-5 data, then performing the FIX-HF-5C analysis (with and without borrowing of FIX-HF-5 data).

1.4.6.12 Comparison of Baseline Characteristics between Subjects Showing Improvement vs. Worsening or No Change on the Primary Endpoint (pVO2)

Baseline characteristics including medications were compared between OPTIMIZER subjects who exhibited a worsening or no change in peak VO_2 values to those who demonstrated an improvement in peak VO2 values of greater than or equal to 2 ml/kg/min. Changes were assessed relative to the median value of peak VO2 for the control group. Results for FIX-HF-5C and FIX-HF-5 pooled are shown in Table 35 below. The only parameter which differentiated patients between these two subgroups was a higher prevalence of diabetes in nonresponders.

Table 35: Baseline Characteristics by Change in Peak VO_2 at 24 weeks (compared to control group median change, ACTIVE subjects only). FIX-HF-5C and FIX-HF-5 Pooled, Median (M)=-0.8 ml/kg/min

Variable	<=M ml/kg/min Mean (SD) or n (%) N=58	>=M+2 ml/kg/min Mean (SD) or n (%) N=56	p-value (2-sided)
Age (yrs)	61.4 (11.5)	60.0 (12.0)	0.5157
Male	41 (70.7%)	43 (76.8%)	0.5264
Ethnicity (White)	46 (79.3%)	44 (78.6%)	1.0000
CHF Etiology (Ischemic)	43 (74.1%)	37 (66.1%)	0.4146
Prior MI	37 (63.8%)	35 (62.5%)	1.0000
Prior ICD	51 (87.9%)	47 (83.9%)	0.5974
Diabetes	35 (60.3%)	22 (39.3%)	0.0389
QRS Duration (ms)	100.5 (13.0)	100.6 (14.0)	0.9884
LVEF (%) (core lab)	31.5 (5.1)	31.6 (4.9)	0.9181
LVEDD (mm) (core lab)	57.9 (7.1)	58.1 (6.1)	0.8763
Weight (kg)	95.7 (21.5)	90.8 (24.8)	0.2644
Height (cm)	173.7 (8.6)	174.1 (11.0)	0.7920
BMI (kg/m2)	31.6 (6.4)	29.6 (6.3)	0.0981
Resting HR (bpm)	70.7 (11.2)	70.0 (11.8)	0.7625
Systolic	119.6 (18.0)	120.0 (16.7)	0.8948
Diastolic	71.4 (10.5)	70.8 (9.9)	0.7634
ACEi or ARB	52 (89.7%)	49 (87.5%)	0.7747
ACE inhibitor	40 (69.0%)	39 (69.6%)	1.0000
ARB	13 (22.4%)	12 (21.4%)	1.0000
Beta Blocker	56 (96.6%)	53 (94.6%)	0.6763
Diuretic	43 (74.1%)	47 (83.9%)	0.2526
Second Diuretic	4 (6.9%)	4 (7.1%)	1.0000

Table 35: Baseline Characteristics by Change in Peak VO_2 at 24 weeks (compared to control group median change, ACTIVE subjects only). FIX-HF-5C and FIX-HF-5 Pooled, Median (M)=-0.8 ml/kg/min

Variable	<=M ml/kg/min Mean (SD) or n (%) N=58	>=M+2 ml/kg/min Mean (SD) or n (%) N=56	p-value (2-sided)
Ivabradine	0 (0.0%)	1 (1.8%)	0.4912
Digoxin	15 (25.9%)	12 (21.4%)	0.6618
ENTRESTO	1 (1.7%)	0 (0.0%)	1.0000
Aldosterone Inhibitor	25 (43.1%)	20 (35.7%)	0.4487
Hydralazine	2 (3.4%)	2 (3.6%)	1.0000
Nitrates	21 (36.2%)	16 (28.6%)	0.4277
Calcium Channel Blocker	4 (6.9%)	7 (12.5%)	0.3569
Anti-arrhythmic	9 (15.5%)	9 (16.1%)	1.0000
Aspirin	39 (67.2%)	45 (80.4%)	0.1382
Coumadin	8 (13.8%)	8 (14.3%)	1.0000
Clopidogrel	16 (27.6%)	12 (21.4%)	0.5168

Program: Responders.sas

1.4.6.13 Secondary Effectiveness Endpoints

1.4.6.13.1 MLWHFQ

Given that the null hypothesis was rejected for the primary effectiveness endpoint, we proceed to the first pre-specified secondary endpoint, MLWHFQ. As described in the SAP, a linear mixed model (non-Bayesian) is fitted on the MLWHFQ endpoint. There are a total of 160 patients and 443 non-missing MLWHFQ observations in FIX-HF-5C for this analysis.

Table 36: Number of Observations, Mean, SD of MLWHFQ by Group and Time

	Nobs(observed)		Nobs(missing)		Mean		Standard Deviation	
	Control	Active	Control	Active	Control	Active	Control	Active
1 (Baseline)	86	74	0	0	57.35	56.42	23.36	22.95
2 (12 wks)	80	71	3	1	49.71	38.34	24.72	23.55
3 (24 wks)	76	70	4	2	47.47	35.26	25.65	24.63

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

Table 37: MLWHFQ Treatment Differences

Time	Estimate	SE	Lower 95%	Upper 95%	P-value (1-sided)
12 weeks	-10.33	2.95	-16.12	-4.55	<0.001
24 weeks	-11.73	2.99	-17.60	-5.86	<0.001

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

The p-value for the comparison of mean MLWHFQ at 24 weeks for active treatment vs. control is <0.001. The null hypothesis is rejected, and active treatment is superior to control with respect to mean MLWHFQ at 24 weeks.

1.4.6.13.2 Change in NYHA from Baseline

Given that the first secondary null hypothesis was rejected, we proceed to the second secondary effectiveness endpoint, which is improvement in heart failure class, as assessed by the New York Heart Association (NYHA) classification. The analysis of this endpoint tests the hypothesis that the subjects treated with the device have greater odds of improving by at least one NYHA category compared to the control group.

Table 38: NYHA: Baseline vs. 24 Weeks

Treatment Group	Baseline NHYA	NYHA at 24 Weeks				Total
		1	2	3	4	
Active	**3**	23 (38%)	25 (42%)	12 (20%)	0 (0%)	60
	4	3 (30%)	4 (40%)	2 (20%)	1 (10%)	10
Control	**3**	12 (18%)	16 (24%)	39 (57%)	1 (1%)	68
	4	0 (0%)	0 (0%)	4 (57%)	3 (3%)	7

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

The p-value for the stratified Cochran Mantel-Haenzel test is < 0.001. The null hypothesis is rejected, and the Active arm is superior to Control.

Table 39: NYHA: Improvement in NYHA, FIX-HF-5C

Etiology	Active	Control	Odds Ratio	P-Value (1-sided)
Ischemic	34/43 (79%)	18/43 (42%)	5.97	< 0.001
Non-Ischemic	23/27 (85%)	14/32 (44%)		

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

A stratified Cochran Mantel-Haenzel test (with strata defined by etiology of heart failure) is used to compute a p-value at the one-sided 0.025 level.

1.4.6.13.3 PeakVO_2 with RER>1.05 Subset

Given that the null hypothesis for NYHA was rejected, we proceed to the third secondary effectiveness endpoint, which is mean peak VO_2 among observations with RER > 1.05. A linear mixed model (non-Bayesian) is fitted on the peak VO_2 endpoint.

There are a total of 160 patients and 420 non-missing peak VO_2 observations in FIX-HF-5C for this analysis.

Table 40: Number of Observations, Mean, SD of Peak VO_2 by Group and Time

	Nobs(observed)		Nobs(missing)		Mean		Standard Deviation	
	Control	Active	Control	Active	Control	Active	Control	Active
1 (Baseline)	83	71	3	3	15.35	15.52	2.82	2.64
2 (12 wks)	68	64	12	7	15.24	15.67	3.07	3.22
3 (24 wks)	69	65	7	5	15.25	15.56	3.21	3.47

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

Table 41: pVO_2 Treatment Differences with RER≥1.05

Time	Estimate	SE	Lower 95%	Upper 95%	P-value (1-sided)
12 weeks	0.35	0.35	-0.33	1.04	0.1570
24 weeks	0.43	0.35	-0.25	1.11	0.1100

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

As seen in Table 40 the trend of the treatment effect is in favor of CCM™ treatment. However, the p-value for the comparison of mean peak VO_2 at 24 weeks for active treatment vs. control among observations with RER >1.05 is 0.099. The null hypothesis is not rejected, and there is insufficient evidence to claim a difference in mean peak VO_2 among observations with RER >1.05 with FIX-HF-5C data alone. However, as will be shown in section 4.4.6.14.3 (pVO_2 with RER≥1.05 Subset by Study) when data were pooled from the FIX-HF-5 and FIX-HF-5C studies, the treatment effect was estimated as 0.62 ml/kg/min with a p value of 0.009.

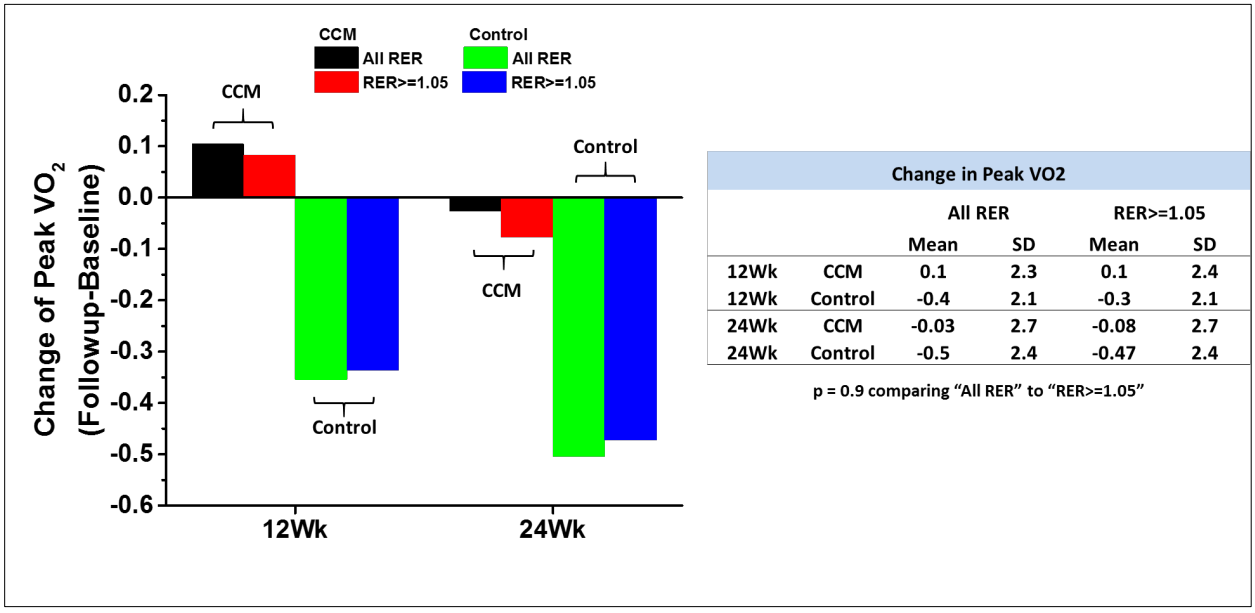
Table 33a shows results from Completed Cases. For this analysis there are a total of 160 patients and 442 non-missing peak VO2 observations from FIX-HF-5C patients. Also, in this analysis, zeros are imputed for deaths in accordance with the prospective statistical analysis plan.

In Table 40, which is an analysis of peak VO_2 for tests in which RER is ≥1.05, there are a total of 160 patients and 420 non-missing values for peak VO_2 observations; 22 subjects less than in Table 33a. In this analysis, zeros are NOT imputed for deaths, which certainly had an important influence on the findings since there were more deaths in Control and Active treatment groups.

In addition to the 10 tests missing due to deaths, there were 12 addition patients in which tests were deemed adequate but in which the RER was <1.05 (6 in the Control group and 6 CCM group).

This accounts for the differences in the number of observations. There are several additional important points for discussion.

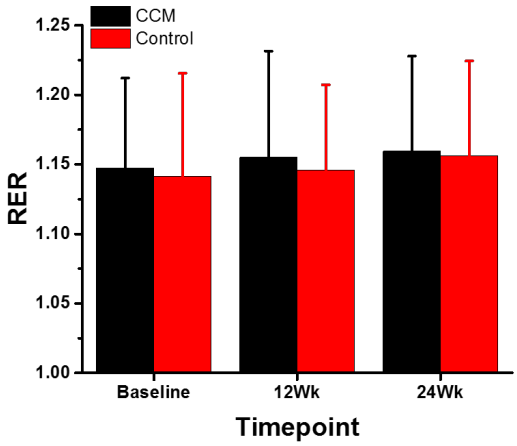
First, despite the reduced number of observations in the analysis that includes only tests with RER≥1.05, the treatment effect still trends in the direction of benefit of CCM treatment. In fact, the sensitivity analysis on the completed cases analysis without any imputation (Table 20) showed treatment benefit with the Bayesian borrowing, and the 24-week difference between treatments in this population is similar to the RER≥1.05 subset. This is further illustrated in the following graph (FIX-HF-5C data) which shows that at each timepoint and both groups, elimination of tests with RER<1.05 has very small effects on the impact of changes in peak VO2 values.



Change in Peak VO2					
		All RER		RER>=1.05	
		Mean	SD	Mean	SD
12Wk	CCM	0.1	2.3	0.1	2.4
12Wk	Control	-0.4	2.1	-0.3	2.1
24Wk	CCM	-0.03	2.7	-0.08	2.7
24Wk	Control	-0.5	2.4	-0.47	2.4

p = 0.9 comparing "All RER" to "RER>=1.05"

More generally, inclusion of an analysis that only uses tests with RER ≥1.05 was required by FDA over counter-arguments of IMPULSE and consultants as was documented in the meeting notes of teleconferences with FDA (Attachment 10). We remain concerned about the physiological and statistical validity of such an analysis. Firstly, a 1.05 RER cutoff is arbitrary and assumes that a patient achieving a lower RER value cannot have reached their exercise limit. Impulse provided a reference showing, from independent analysis, that low RER values are associated with a patient's maximum effort and that increases of RER may themselves reflect improvements in patient conditions. Accordingly, this analysis throws away one side of the distribution that contributes to the assessment of the treatment effect. Furthermore, all the unprecedented safeguards introduced in the conduct, data collection and interpretation of test results discussed were geared to minimizing (if not eliminating) possible placebo effects on peak VO_2. As evidence of the success of the approach, please refer to the following graph of data from the FIX-HF-5C, which shows the average RER of tests at each timepoint by group. As seen, there is no difference over time or between groups (p>0.4 for all comparisons).



RER averages over time

	CCM	SD	Control	SD
Baseline	1.15	0.06	1.14	0.07
12 Weeks	1.16	0.08	1.15	0.06
24 Weeks	1.16	0.07	1.16	0.07

Thus, using RER as in an index, there is no evidence of change of effort during exercise testing in either group.

In summary, the impact of removing test results with RER <1.05 has only a small effect on the time course of change of peak VO2 in both groups. We have further shown that based on the FDA-specified index (i.e., RER) there is no evidence of change in effort on exercise testing over time in either group, which is likely a result of the unprecedented and extreme measures taken to ensure test quality in this study. We reiterate concerns stated during deliberations with FDA that throwing out valid data with RER values between 1.00 and 1.05 is not the proper way to handle the question of change in patient effort from physiological or statistical perspectives. Finally, we are not aware of any prior study in which

such criteria have been applied to the analysis of clinical trial results; there is no precedent for performing or interpreting the results of such an analysis.

1.4.6.13.4 Effectiveness Endpoint Summary

Results demonstrate superiority of the OPTIMIZER group over the control group with respect to peak VO_2, quality of life (MLWHFQ), and NYHA Class. All three are important indicators of heart failure severity and improvement in these parameters in the subject population of moderately severe heart failure patients is strong evidence for a physiologic effect of CCM™ therapy.

1.4.6.14 Secondary Sensitivity Analyses by Study

1.4.6.14.1 MLWHFQ Sensitivity by Study

Estimates of changes in MLWHFQ in the FIX-HF-5 and FIX-HF-5C studies alone and combined (i.e., data pooled from both studies) are summarized in Tables 42-44 and Fig. 17. MLWHFQ improved more in the Treatment group of each of the studies (by approximately 11 points) as well as in the pooled data.

Table 42: MLWHFQ Treatment Differences, FIX-HF-5

Time	Estimate	SE	Lower 95%	Upper 95%	P-value (1-sided)
12 weeks	-12.59	2.45	-17.38	-7.79	<0.001
24 weeks	-10.82	2.42	-15.57	-6.07	<0.001

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

Table 43: MLWHFQ Treatment Differences, FIX-HF-5C

Time	Estimate	SE	Lower 95%	Upper 95%	P-value (1-sided)
12 weeks	-10.33	2.95	-16.12	-4.55	<0.001
24 weeks	-11.73	2.99	-17.60	-5.86	<0.001

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

Table 44: MLWHFQ Treatment Differences, FIX-HF-5/5C, Combined

Time	Estimate	SE	Lower 95%	Upper 95%	P-value (1-sided)
12 weeks	-11.44	1.89	-15.15	-7.74	<0.001
24 weeks	-10.90	1.89	-14.61	-7.19	<0.001

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

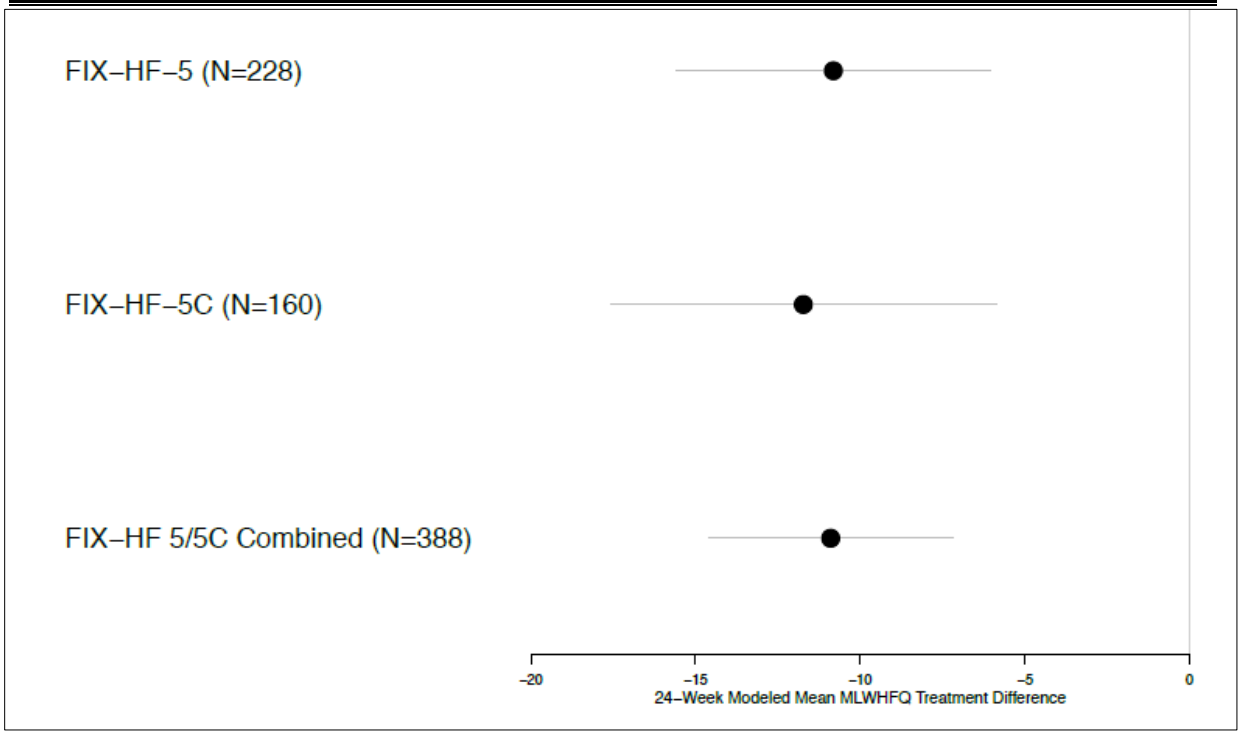


Figure 17: 24-Week Modeled MLWHFQ Treatment Difference by Study

1.4.6.14.2 NYHA Sensitivity by Study

Estimates of changes in NYHA in the FIX-HF-5 and FIX-HF-5C studies alone and combined (i.e., data pooled from both studies) are summarized in Tables 45-47. In each study, and in the combined dataset, a greater proportion of patients NYHA improved by 1 or more classes in the Treatment group compared to Controls as well as in the pooled data. This was the case for both Ischemic and Non-Ischemic heart failure etiology. From the pooled data, Treatment patients were 2.85 times more likely to experience an improved NYHA than Controls.

Table 45: Improvement in NYHA, FIX-HF-5

Etiology	Active	Control	OddsRatio	P-value (1-sided)
Ischemic	37/73 (51%)	11/61 (18%)	2.05	0.01
Non-Ischemic	10/30 (33%)	16/33 (48%)		

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

Table 46: Improvement in NYHA, FIX-HF5C

Etiology	Active	Control	OddsRatio	P-value (1-sided)
Ischemic	34/43 (79%)	18/43 (42%)	5.97	< 0.001
Non-Ischemic	23/27 (85%)	14/32 (44%)		

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

Table 47: Improvement in NYHA, FIX-HF 5/5C Combined

Etiology	Active	Control	OddsRatio	P-value (1-sided)
Ischemic	71/116 (61%)	29/104 (28%)	2.85	< 0.001
Non-Ischemic	33/57 (58%)	30/65 (46%)		

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

1.4.6.14.3 pVO_2 with RER≥1.05 Subset by Study

Estimates of changes in peak VO_2 in the subset of tests in which RER was ≥1.05 in the FIX-HF-5 and FIX-HF-5C studies alone and combined (i.e., data pooled from both studies) are summarized in Tables 48-50 and Fig. 18. In this subset of tests, peak VO_2 trended to improve more in the Treatment group of each of the studies and was statistically significant in the FIX-HF-5 study alone. In addition, this parameter was significantly improved by 0.62 ml/kg/min in the pooled data.

Table 48: pVO_2 Treatment Differences with RER ≥ 1.05, FIX-HF-5

Time	Estimate	SE	Lower 95%	Upper 95%	P-value (1-sided)
12 weeks	0.00	0.40	-0.79	0.78	0.5020
24 weeks	0.83	0.39	0.06	1.61	0.0170

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

Table 49: pVO_2 Treatment Differences with RER ≥ 1.05, FIX-HF-5C

Time	Estimate	SE	Lower 95%	Upper 95%	P-value (1-sided)
12 weeks	0.35	0.35	-0.33	1.04	0.1570
24 weeks	0.43	0.35	-0.25	1.11	0.1100

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

Table 50: pVO_2 Treatment Differences with RER ≥ 1.05, FIX-HF-5/5C, Combined

Time	Estimate	SE	Lower 95%	Upper 95%	P-value (1-sided)
12 weeks	0.18	0.27	-0.35	0.70	0.2530
24 weeks	0.62	0.26	0.11	1.14	0.0090

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

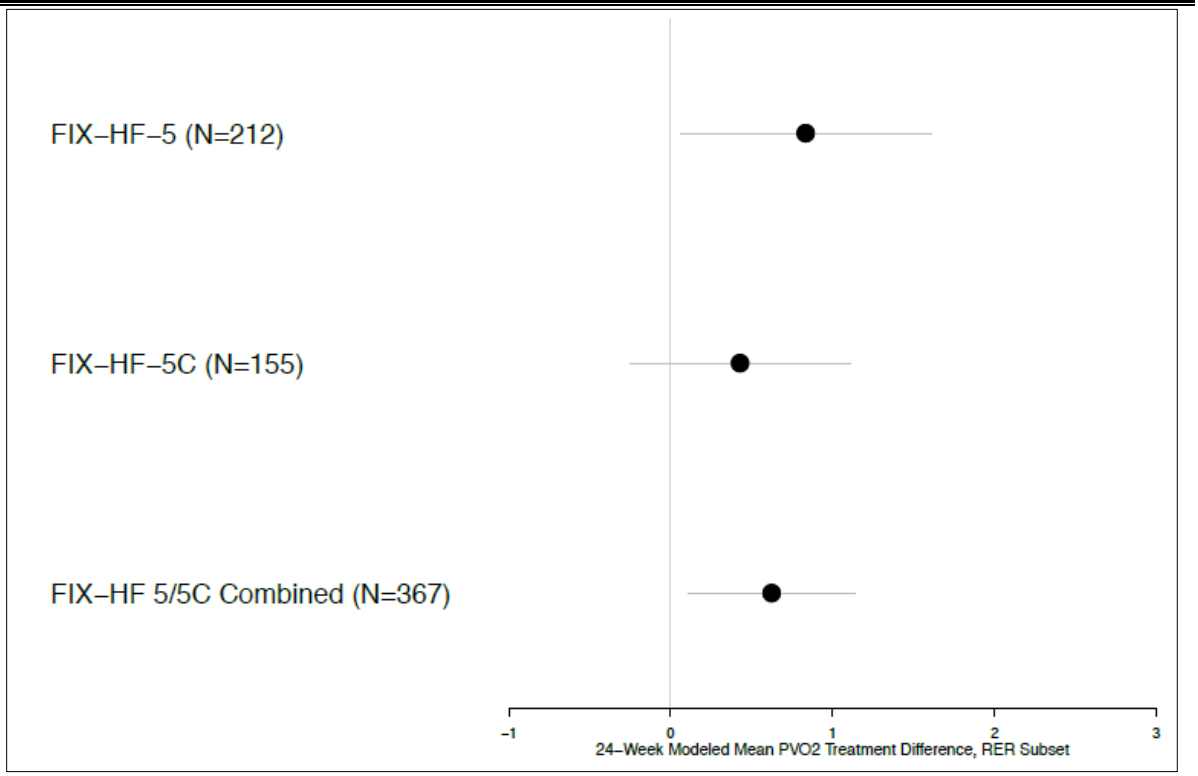


Figure 18: 24-Week Modeled Mean pVO_2 Treatment Difference with RER≥1.05 subset by Study

1.4.6.15 Secondary Sensitivity Analyses: Per Protocol Population

1.4.6.15.1 MLWHFQ Sensitivity: Per Protocol (PP) Population

There was a total of 154 patients and 445 non-missing MLWHFQ observations in FIX-HF-5C for this analysis as summarized in Table 51. The treatment effect in the PP population was -12.32 points (Table 52).

Table 51: Number of Observations, Mean, SD of MLWHFQ by Group and Time

	Nobs(observed)		Nobs(missing)		Mean		Standard Deviation	
	Control	Active	Control	Active	Control	Active	Control	Active
1 (Baseline)	86	68	0	0	57.35	55.40	23.36	23.42
2 (12 wks)	80	68	3	0	49.71	37.13	24.72	23.21
3 (24 wks)	76	67	4	1	47.47	34.18	25.65	24.44

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

Table 52: MLWHFQ Treatment Differences

Time	Estimate	SE	Lower 95%	Upper 95%	P-value (1-sided)
12 weeks	-11.05	3.01	-16.95	-5.16	<0.001
24 weeks	-12.32	3.05	-18.29	-6.35	<0.001

1.4.6.15.2 NYHA Sensitivity: Per Protocol Population

The number and percentage of patients in each NYHA class at 24 weeks as a function of baseline NYHA is summarized in Table 53. As summarized in Table 54, patients in the Treatment group were significantly more likely to experience an improved NYHA class than patients in the Control group.

Table 53: NYHA: Baseline vs. 24 Weeks

Treatment Group	Baseline NHYA	NYHA at 24 Weeks				Total
		1	2	3	4	
Active	3	23 (40%)	24 (41%)	11 (19%)	0 (0%)	58
	4	3 (33%)	4 (44%)	1 (11%)	1 (11%)	9
Control	3	12 (18%)	16 (24%)	39 (57%)	1 (1%)	68
	4	0 (0%)	0 (0%)	4 (57%)	3 (43%)	7

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

Table 54: Improvement in NYHA

Etiology	Active	Control	OddsRatio	P-value (1-sided)
Ischemic	33/41 (80%)	18/43 (42%)	6.21	< 0.001
Non-Ischemic	22/26 (85%)	14/32 (44%)		

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

1.4.6.15.3 pVO_2 with RER≥1.05 Subset Sensitivity: Per Protocol Population

There was a total of 154 patients and 410 non-missing Peak VO_2 observations with RER≥1.05 in FIX-HF-5C PP population for this analysis (Table 55). Results in the PP population are similar to those of the Intent to Treat population (Table 56).

Table 55: Number of Observations, Mean, SD of Peak VO2 with RER≥1.05 by Group and Time

	Nobs(observed)		Nobs(missing)		Mean		Standard Deviation	
	Control	Active	Control	Active	Control	Active	Control	Active
1 (Baseline)	83	65	3	3	15.35	15.57	2.82	2.61
2 (12 wks)	68	62	12	6	15.24	15.68	3.07	3.27
3 (24 wks)	69	63	7	4	15.25	15.55	3.21	3.51

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

Table 56: pVO_2 Treatment Differences with RER ≥ 1.05

Time	Estimate	SE	Lower 95%	Upper 95%	P-value (1-sided)
12 weeks	0.35	0.35	-0.34	1.04	0.1610
24 weeks	0.40	0.35	-0.28	1.09	0.1250

Program: FIX5C-Analysis-ImpulseDynamics-UpdatedDataRev.Rnw

1.4.6.16 Primary Safety Endpoint

The primary safety endpoint is the composite endpoint of the percentage of subjects in the OPTIMIZER group who experienced either an OPTIMIZER device or OPTIMIZER procedure related complication through the 24-week follow-up period, as determined by an independent events adjudication committee (EAC). The EAC reviewed all serious adverse event reports (SAEs), confirmed the classification of "serious", and adjudicated the relationship of the event to the OPTIMIZER System device or procedure. SAEs that the EAC determined to be definitely related to either the OPTIMIZER System or the OPTIMIZER Procedure were further classified as either a Complication or Not a Complication. A "complication" was defined as an OPTIMIZER device or OPTIMIZER procedure related event that requires invasive treatment or results in a permanent disability or death. Satisfying the primary safety endpoint required that the complication-free proportion of patients was significantly higher than 70% (using a one-sided significance level of 0.025).

Only those subjects that underwent the OPTIMIZER implant procedure could experience an OPTIMIZER procedure related complication and only those subjects who receive the OPTIMIZER device could experience an OPTIMIZER device related complication. Thus, the "As Treated" cohort is the primary cohort for analysis. The per protocol population is also presented, however, this population is identical to the as treated population for OPTIMIZER subjects in the FIX-HF-5C study. For completeness, results in the intent to treat population are also provided.

Table 57: Primary Safety Endpoint[1] Analysis (OPTIMIZER Group Only)

Population	Complication Free Rate x/n (%)	95% LCL (%)	95% UCL (%)
As Treated	61/68 (89.7%)	79.9%	95.8%
Per Protocol	61/68 (89.7%)	79.9%	95.8%
ITT	67/74 (90.5%)	81.5%	96.1%

Program: Safety Primary.sas

[1] OPTIMIZER subjects experiencing a device related and or procedure related adverse event.

Thus, the complication free proportion in the as treated study group is 89.7% (61/68) with lower confidence limit of 79.9% (one-sided alpha=0.025). As this is greater than the pre-defined threshold of 70%, the primary safety endpoint was met. The ITT analysis yields similar results (90.5% (67/74) with lower confidence limit of 81.5%) and the PP analysis was identical.

1.4.6.17 Secondary Safety Endpoints

There are five secondary safety endpoints: overall survival through 24 weeks, cardiac death survival through 24 weeks, freedom from all-cause mortality or all-

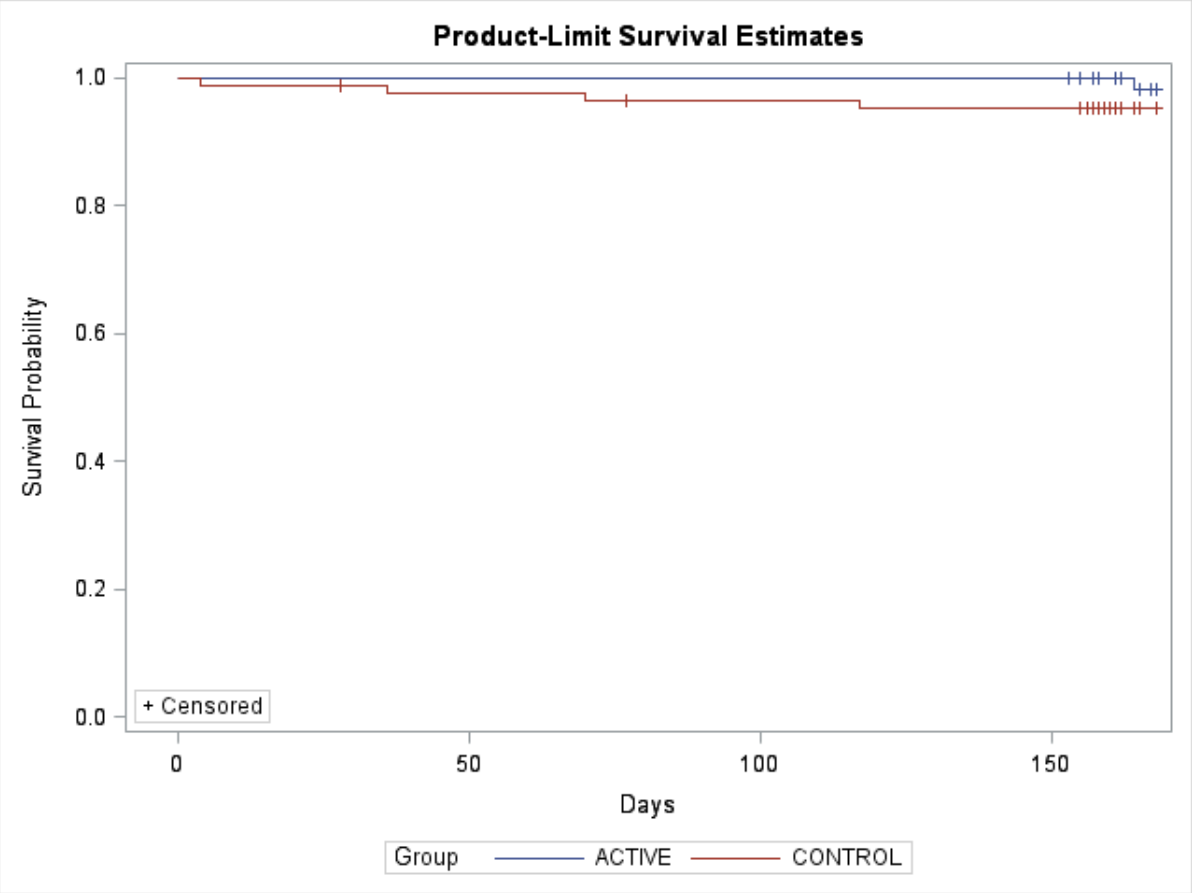
cause hospitalization through 24 weeks, freedom from cardiac death and worsening heart failure hospitalization through 24 weeks and adjudicated serious adverse events by treatment group through 24 weeks. The survival analyses and freedom from event analysis were based on Kaplan-Meier analysis and the adverse events are tabulated by seriousness and treatment group with testing by Fisher's exact test.

1.4.6.17.1 Survival Analyses

The following section (section 4.4.6.17.1.a) provides results of various survival analyses performed on data derived exclusively on the FIX-HF-5C study cohort. Pooling data from the FIX-HF-5 subgroup and the FIX-HF-5C study resulted in a significantly larger sample size. Results from the combined population are provided in section 4.4.6.17.1.b. below.

a. Survival Analyses through 24 Weeks (FIX-HF-5C PP Population)

The plot of the Kaplan-Meier analysis of **overall survival** in the FIX-HF-5C study is presented in the figure below and results are summarized in Table 58. The two-groups are similar with respect to overall survival from baseline through 24 weeks (98% in Treatment vs 95% in Control, log-rank P= 0.2549).



Program: Safety Survival Analyses.sas

P-value: 2-sided

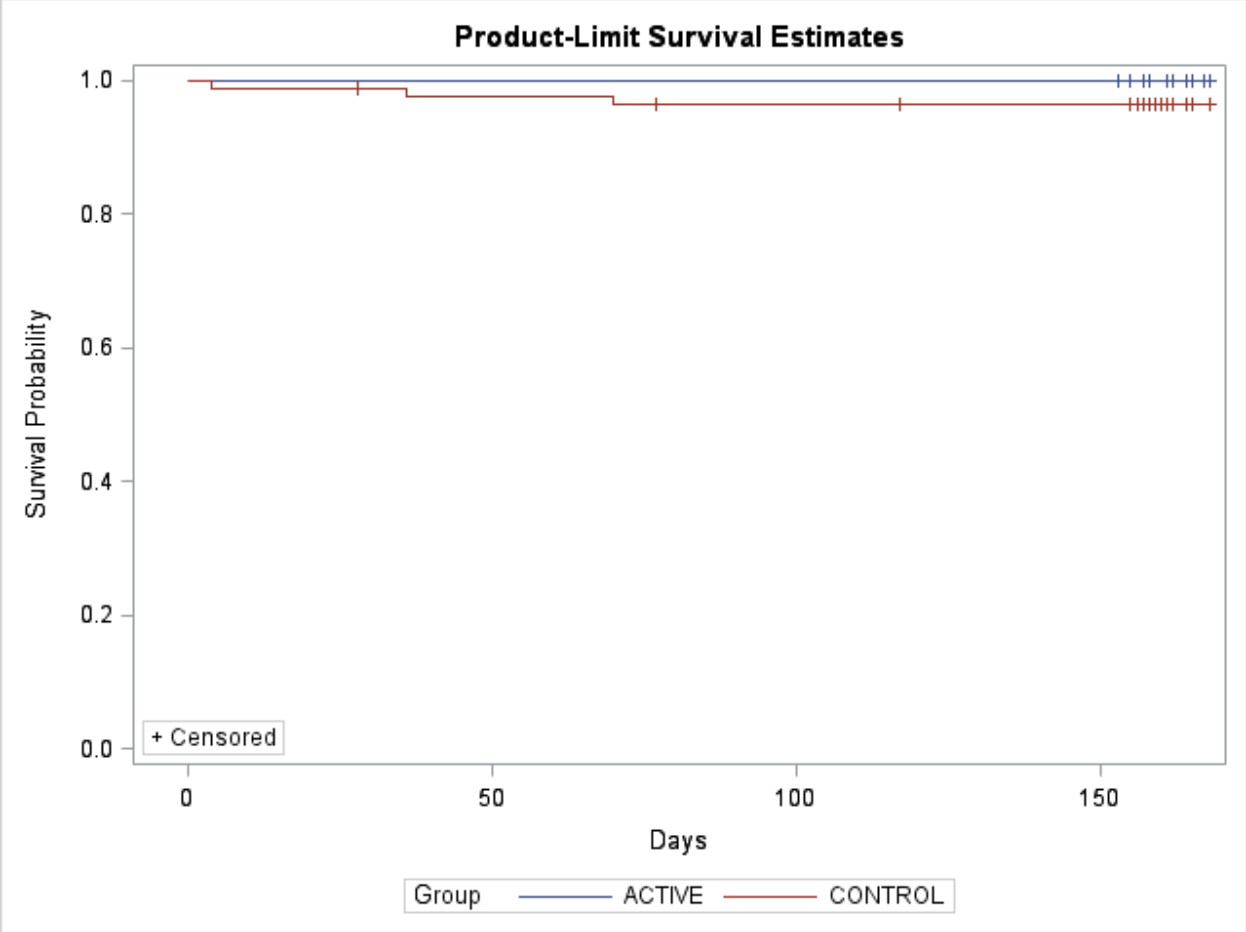
Figure 19: Overall Survival through 24 Weeks by Treatment Group by Kaplan-Meier Analysis

Table 58: Overall Survival through 24 Weeks

Treatment Group	Time	Number at Risk	Total Number Failed	Proportion Surviving	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Active	0 Weeks	68	0	1.0000	--	--
	12 Weeks	68	0	1.0000	--	--
	24 Weeks	54	1	0.9828	0.8838	0.9976
Controls	0 Weeks	86	0	1.0000	--	--
	12 Weeks	81	3	0.9648	0.8949	0.9885
	24 Weeks	62	4	0.9529	0.8794	0.9821
Log-rank P= 0.2549 (2-sided)						

Program: Safety Survival Analyses.sas

The Kaplan-Meier plot of freedom from **cardiac death** in the FIX-HF-5C study is presented in the figure below and summarized in Table 59. Similar to the overall survival, the two-groups are similar with respect to survival free of cardiac death from baseline through 24 weeks (100% in Treatment vs 96% in Control, log-rank P= 0.1198).



Program: Safety Survival Analyses.sas
P-value: 2-sided

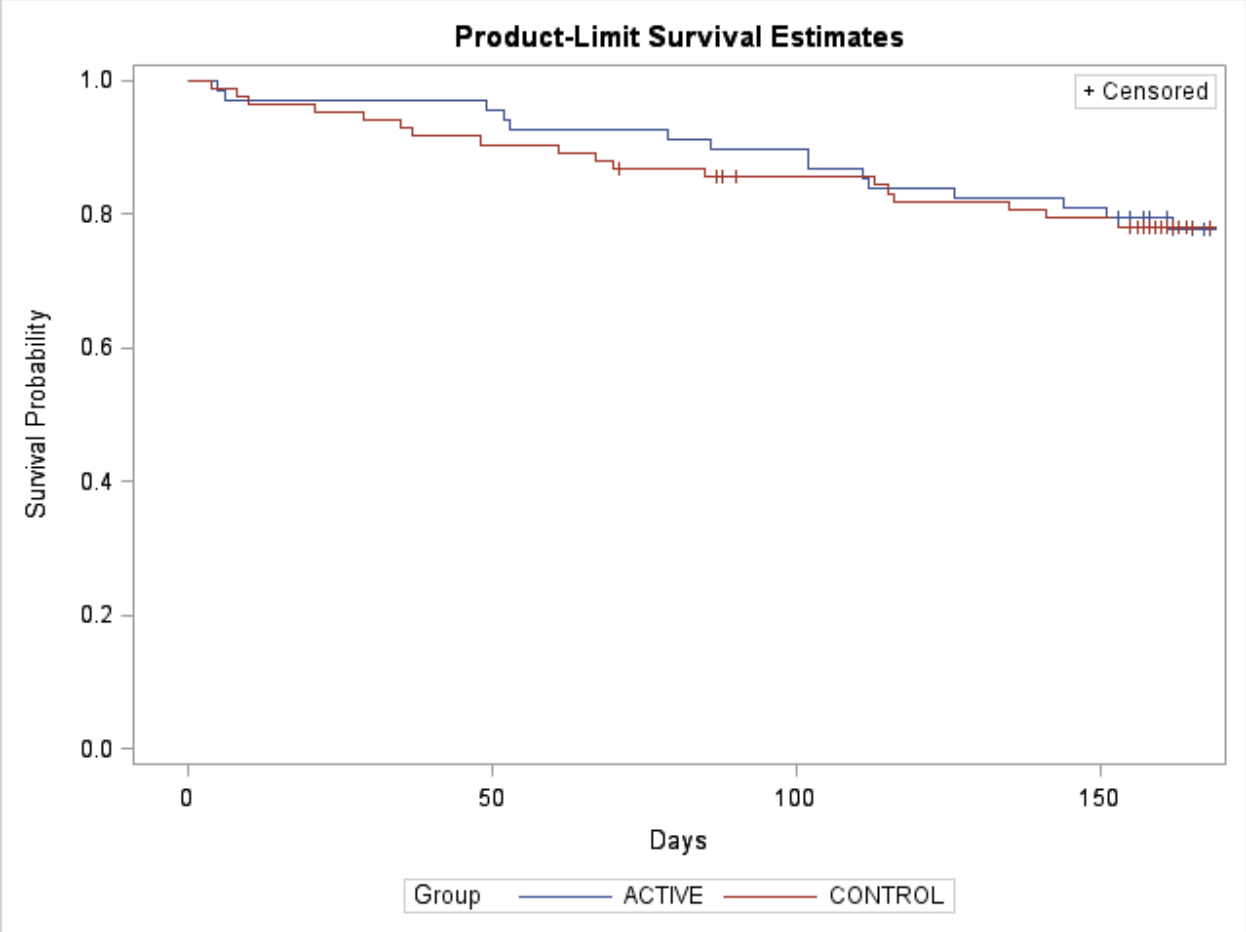
Figure 20: Survival from Cardiac Death through 24 Weeks by Treatment Group by Kaplan-Meier Analysis

Table 59: Survival Free of Cardiac Death through 24 Weeks

Treatment Group	Time	Number at Risk	Total Number Failed	Proportion Surviving	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Active	0 Weeks	68	0	1.0000	--	--
	12 Weeks	68	0	1.0000	--	--
	24 Weeks	54	0	1.0000	--	--
Controls	0 Weeks	86	0	1.0000	--	--
	12 Weeks	81	3	0.9648	0.8949	0.9885
	24 Weeks	62	3	0.9648	0.8949	0.9885
Log-rank P= 0.1198 (2-sided)						

Program: Safety Survival Analyses.sas

The Kaplan-Meier plot of the freedom from **all-cause mortality or all-cause hospitalization** in the FIX-HF-5C study is presented in Figure 21 and summarized in Table 60. The proportion surviving was similar for the two groups through 24 weeks (78% in Treatment vs 78% in Control, log-rank P= 0.9437).



Program: Safety Survival Analyses.sas
P-value: 2-sided

Figure 21: Survival from All Cause Death or Hospitalization through 24 Weeks by Treatment Group by Kaplan-Meier Analysis

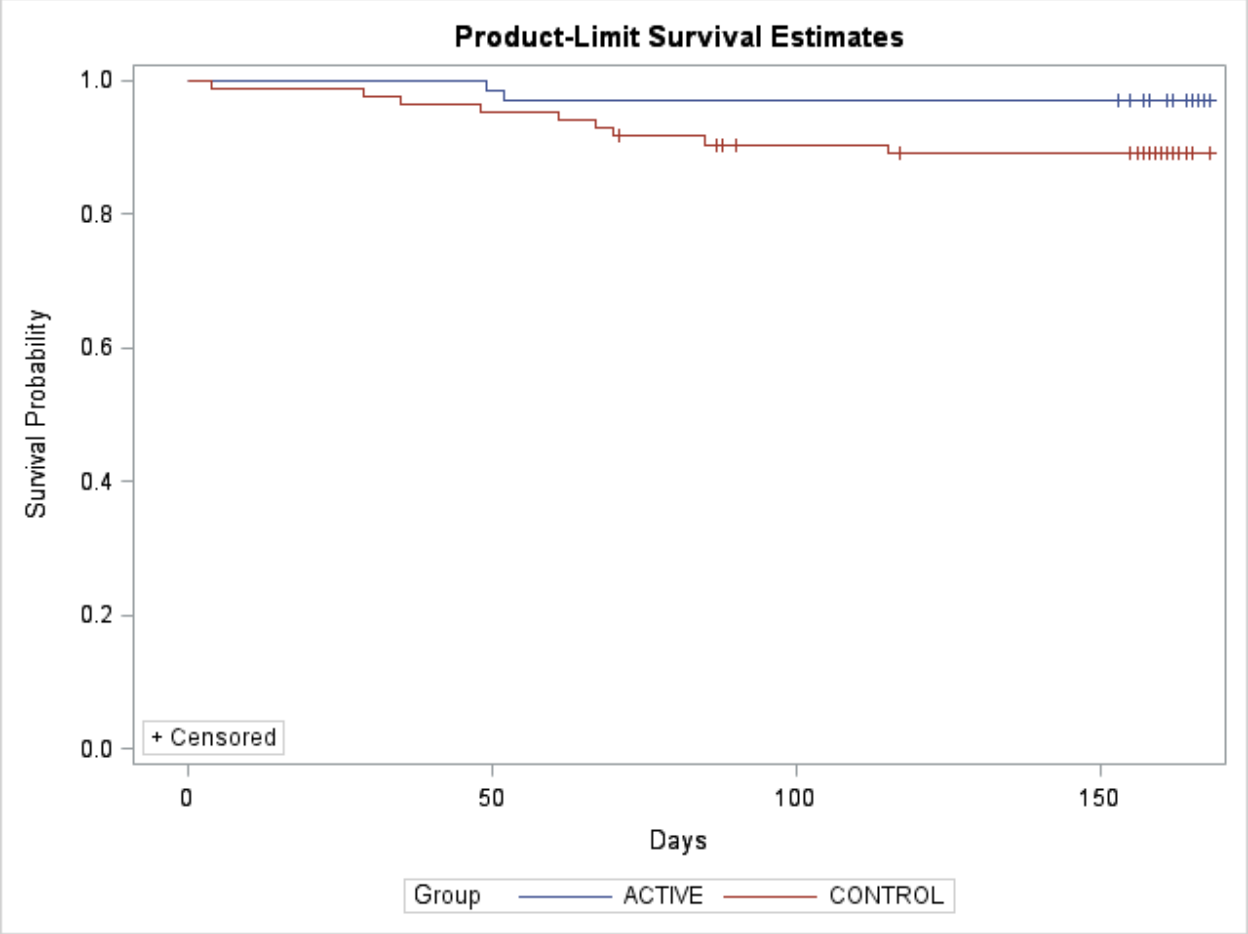
Table 60: Survival from All Cause Death or Hospitalization through 24 Weeks

Treatment Group	Time	Number at Risk	Total Number Failed	Proportion Surviving	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Active	0 Weeks	68	0	1.0000	--	--
	12 Weeks	62	6	0.9118	0.8141	0.9594
	24 Weeks	40	15	0.7769	0.6571	0.8591
Controls	0 Weeks	84	0	1.0000	--	--
	12 Weeks	72	11	0.869	0.776	0.9252
	24 Weeks	38	18	0.7814	0.6754	0.8563
Log-rank P= 0.9437 (2-sided)						

Program: Safety Survival Analyses.sas

The Kaplan-Meier plot of **freedom from cardiac death or worsening heart failure hospitalization** in the FIX-HF-5C study is presented in the figure below and summarized in Table 61. OPTIMIZER Treatment patients had a trend towards better survival from cardiac death or heart failure hospitalizations from baseline through 24 weeks (log-rank P= 0.0665) as can be seen in the figure above and table below, but the result was not statistically significant.

Comparing the Kaplan-Meier rates at 24 weeks, 97.1% versus 89.2%, and using Greenwood's formula for the variance, the difference between treatment and control is 7.9% (95% CI: 0.08%, 15.6%, p=0.048).



Program: Safety Survival Analyses.sas

P-value: 2-sided

Figure 22: Survival from Cardiac Death or Heart Failure Hospitalization through 24 Weeks by Treatment Group by Kaplan-Meier Analysis

Table 61: Survival Free of Cardiac Death or Heart Failure Hospitalization through 24 Weeks

Treatment Group	Time	Number at Risk	Total Number Failed	Proportion Surviving	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Active	0 Weeks	68	0	1.0000	--	--
	12 Weeks	66	2	0.9706	0.8875	0.9926
	24 Weeks	50	2	0.9706	0.8875	0.9926
Controls	0 Weeks	84	0	1.0000	--	--
	12 Weeks	76	7	0.9167	0.8331	0.9594
	24 Weeks	43	9	0.8920	0.8027	0.9423
Log-rank P= 0.0665 (2-sided)						

Program: Safety Survival Analyses.sas

Importantly, it was determined that the total number of days alive free of hospitalization for heart failure ($DAOOH_{HF}$) was significantly greater in the CCM™ Active treatment group compared with Controls during the 24-week (168 day) study period. This analysis accounted for minor differences in duration of follow-up (due to the ±2 week window for the final visit at 24 weeks) by first expressing $DAOOH_{HF}$ as a percentage of total "follow-up days," where the number of follow-up days was defined as the number of days between the study start date to the date of the final follow-up visit; for patients who died before the end of the study, 168 days was used as the total days of follow up. Final results were then obtained by multiplying the percent $DAOOH_{HF}$ by 168. As summarized above, in the FIX-HF-5C study population, there were very few deaths or heart failure hospitalizations. Accordingly, $DAOOH_{HF}$ in the CCM Treatment group was 167.7±2.2 days, versus 158.3±35.8 days in the Control group (p=0.011), for a difference of 9.4 days.

In addition to $DAOOH_{HF}$, we also explored the rates of hospitalizations for the year prior to study enrollment to the rate during the 24-week study period. The results expressed as events per patient-year are summarized in the following table for both non-heart failure cardiovascular ("CARDIAC") and heart failure (HF) hospitalizations are summarized in the following table. As summarized in the table, although there were imbalances in the event-rates between groups at baseline, both CARDIAC and HF event rates were significantly and substantially reduced during the study period compared to the event rates prior to the study in the Active treatment group but were unchanged in Control group.

Table 62: Summary of cardiovascular and heart failure hospitalizations

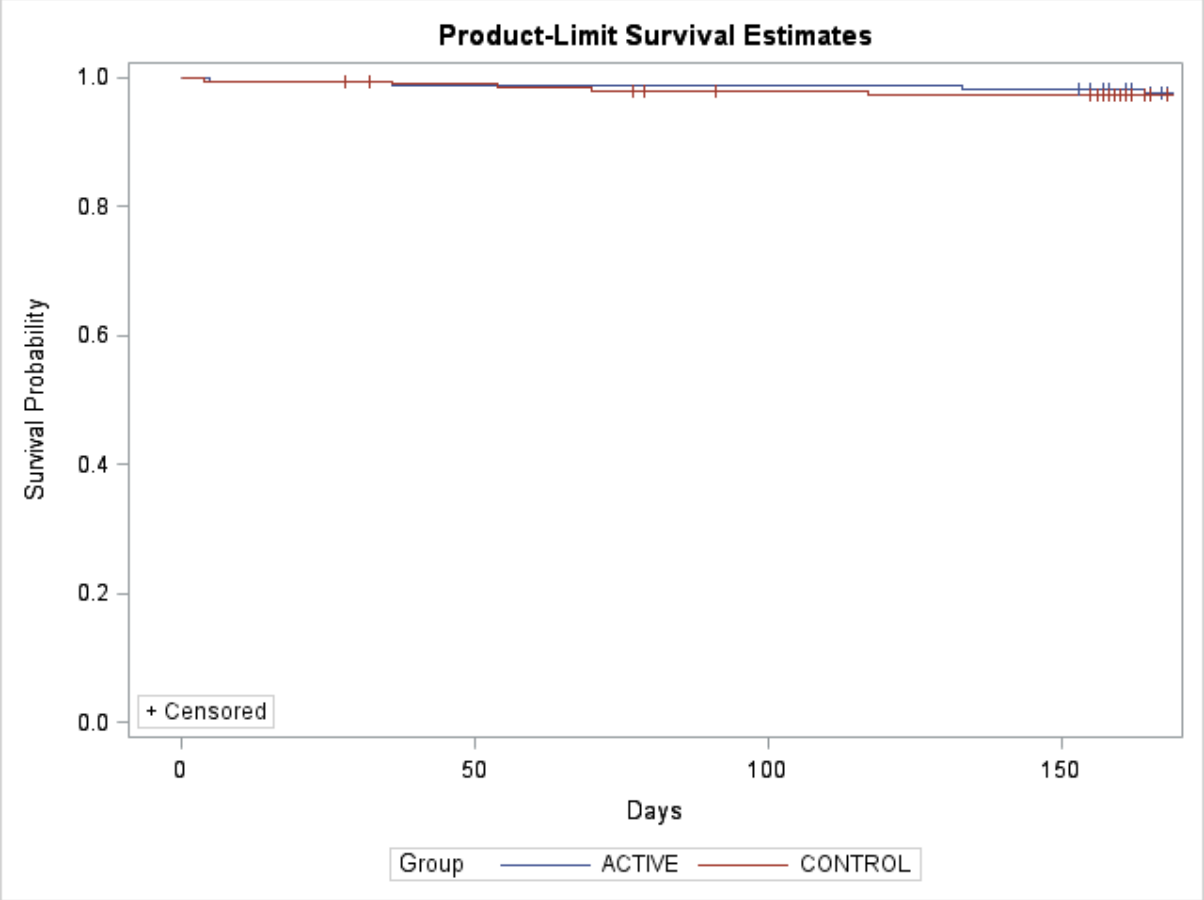
		PRE-Study			POST Study Start Date			
Type	**Group**	**Patient-Yrs**	**Number of Events**	**Event-Rate**	**Patient-Yrs**	**Number of Events**	**Event-Rate**	**p-value (2-sided)**
CARDIAC	**ACTIVE (n=72)**	72.0	80	1.11	31.8	14	0.44	0.0036
	CONTROL (n=81)	81.0	53	0.65	35.6	14	0.39	0.1256
HF	**ACTIVE (n=72)**	72.0	58	0.81	31.8	4	0.13	0.0014
	CONTROL (n=81)	81.0	30	0.37	35.6	11	0.31	0.6155

Program: Pre versus Post Hospitalizations.sas

This analysis was only possible for the FIX-HF-5C study since information about hospitalizations prior to randomization was not available for the FIX-HF-5 study.

b. Survival Analyses through 24 Weeks (PP Population) – Pooled

The plot of the Kaplan-Meier analysis of **overall survival** in the pooled FIX-HF-5 and FIX-HF-5C data is presented in the figure below. The two-groups are similar with respect to overall survival from baseline through 24 weeks (log-rank P= 0.8138).



Program: Safety Survival Analyses.sas
P-value: 2-sided

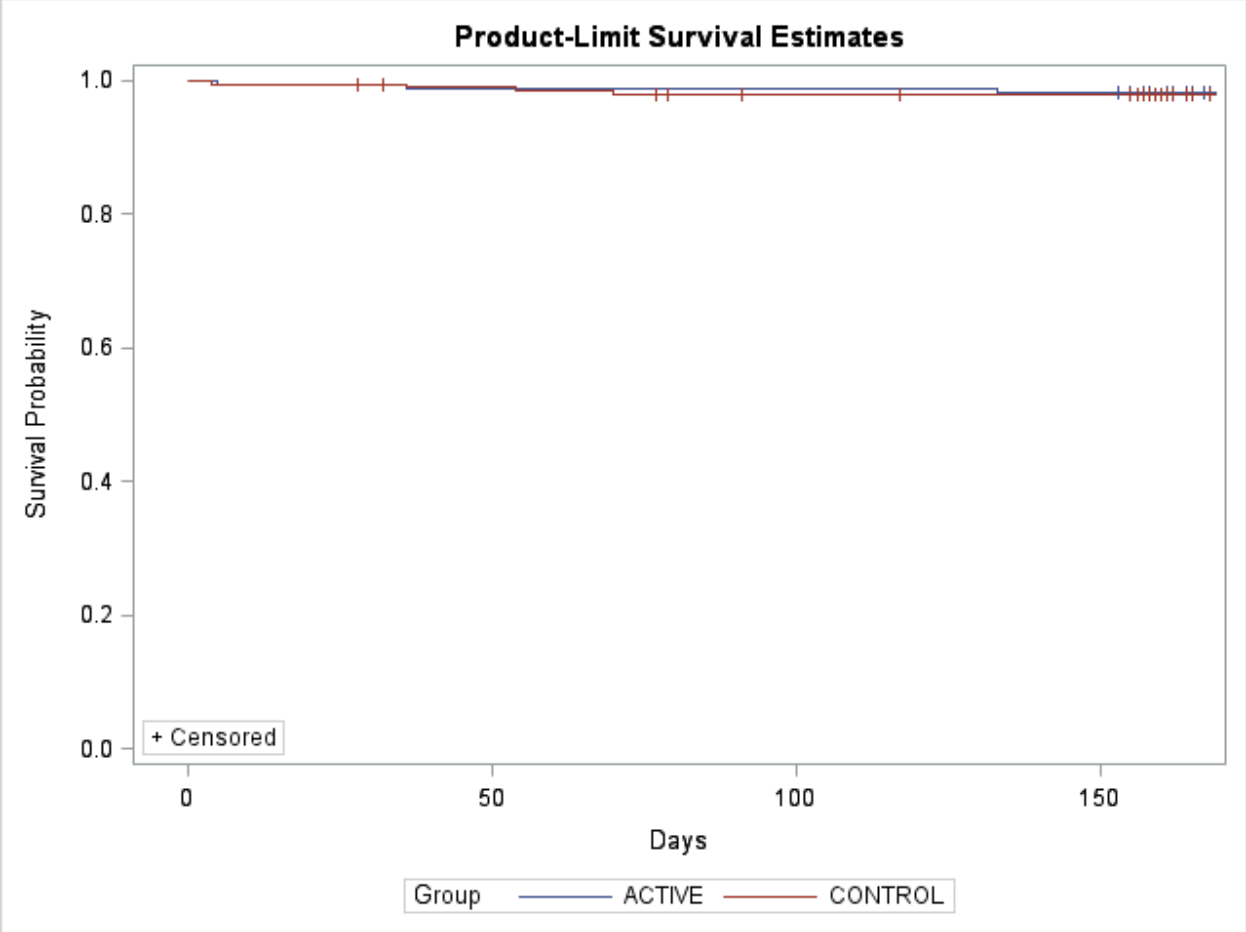
Figure 23: Overall Survival through 24 Weeks by Treatment Group by Kaplan-Meier Analysis

Table 63: Overall Survival through 24 Weeks

Treatment Group	Time	Number at Risk	Total Number Failed	Proportion Surviving	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Active	0 Weeks	177	0	1.0000	--	--
	12 Weeks	175	2	0.9887	0.9556	0.9972
	24 Weeks	160	4	0.9771	0.9400	0.9913
Controls	0 Weeks	193	0	1.0000	--	--
	12 Weeks	185	4	0.9791	0.9453	0.9921
	24 Weeks	165	5	0.9738	0.9382	0.989
Log-rank P= 0.8138 (2-sided)						

Program: Safety Survival Analyses.sas

The Kaplan-Meier plot of **cardiac death** survival in the pooled FIX-HF-5 and FIX-HF-5C data is presented in the figure below.



Program: Safety Survival Analyses.sas

P-value: 2-sided

Figure 24: Survival from Cardiac Death through 24 Weeks by Treatment Group by Kaplan-Meier Analysis

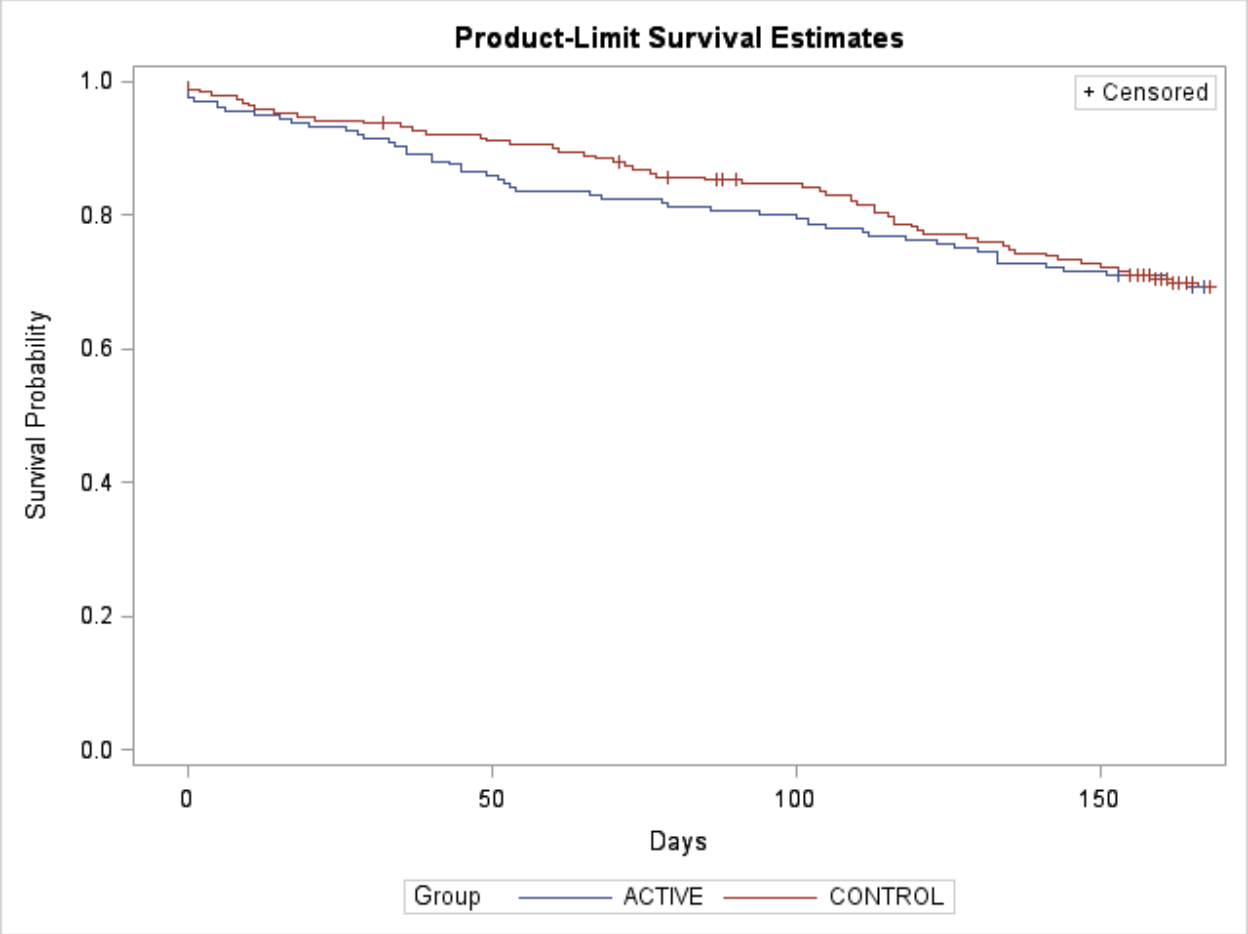
Similar to overall survival, the two-groups are similar with respect to survival from cardiac death from baseline through 24 weeks (log-rank P= 0.7786).

Table 64: Survival from a Cardiac Death through 24 Weeks

Treatment Group	Time	Number at Risk	Total Number Failed	Proportion Surviving	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Active	0 Weeks	177	0	1.0000	--	--
	12 Weeks	175	2	0.9887	0.9556	0.9972
	24 Weeks	160	3	0.9831	0.9484	0.9945
Controls	0 Weeks	193	0	1.0000	--	--
	12 Weeks	185	4	0.9791	0.9453	0.9921
	24 Weeks	165	4	0.9791	0.9453	0.9921
Log-rank P= 0.7786 (2-sided)						

Program: Safety Survival Analyses.sas

The Kaplan-Meier plot of the freedom from **all-cause mortality or all-cause hospitalization** in the pooled FIX-HF-5 and FIX-HF-5C data is presented in the figure below. The survival proportions for the two treatment groups are similar through 24 weeks (log-rank P= 0.8615) as further summarized in Table 65.



Program: Safety Survival Analyses.sas

P-value: 2-sided

Figure 25: Survival from All Cause Death or Hospitalization through 24 Weeks by Treatment Group by Kaplan-Meier Analysis

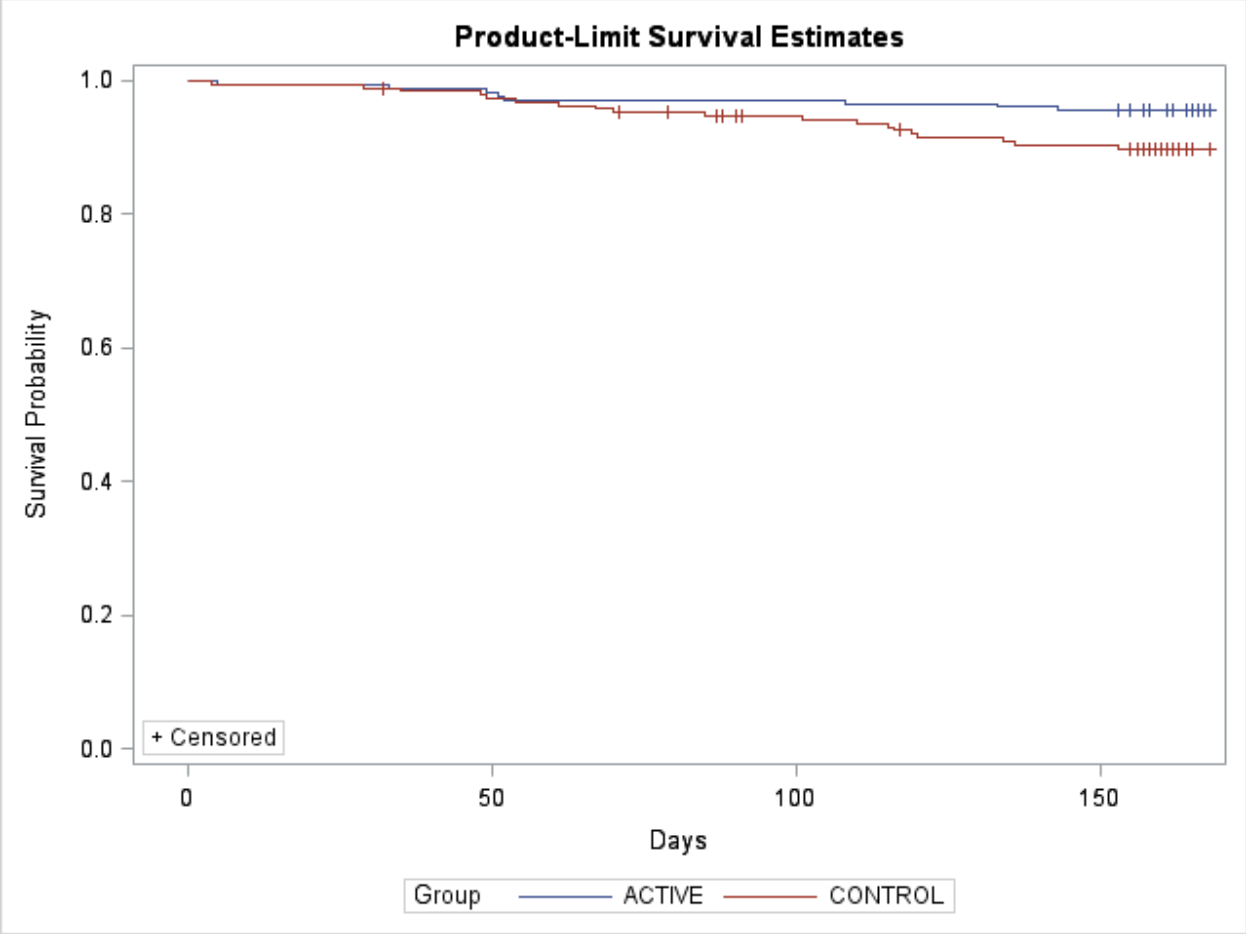
Table 65: Survival from All Cause Death or Hospitalization through 24 Weeks

Treatment Group	Time	Number at Risk	Total Number Failed	Proportion Surviving	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Active	0 Weeks	177	4	0.9774	0.9409	0.9915
	12 Weeks	144	33	0.8136	0.748	0.8636
	24 Weeks	110	54	0.6938	0.6199	0.7561
Controls	0 Weeks	191	2	0.9895	0.9588	0.9974
	12 Weeks	161	27	0.8581	0.7999	0.9004
	24 Weeks	104	57	0.6928	0.6207	0.754

Treatment Group	Time	Number at Risk	Total Number Failed	Proportion Surviving	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Log-rank P= 0.8615 (2-sided)						

Program: Safety Survival Analyses.sas

The Kaplan-Meier plots for the freedom from **cardiovascular death or worsening heart failure hospitalization** in the pooled FIX-HF-5 and FIX-HF-5C data is presented in the figure below.



Program: Safety Survival Analyses.sas
P-value: 2-sided

Figure 26: Survival from Cardiovascular Death or Heart Failure Hospitalization through 24 Weeks by Treatment Group by Kaplan-Meier Analysis

OPTIMIZER subjects had better survival from cardiovascular death or heart failure from baseline through 24 weeks (log-rank P= 0.0419) as can be seen in the figure above and Table 66 below.

Comparing the Kaplan-Meier rates at 24 weeks 95.5% versus 89.8% and using Greenwood's formula for the variance, the difference between treatment and control is 5.7% (95% CI: 0.4%, 11.0%, p=0.036).

Table 66: Survival from Cardiovascular Death or Heart Failure Hospitalization through 24 Weeks

Treatment Group	Time	Number at Risk	Total Number Failed	Proportion Surviving	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Active	0 Weeks	177	0	1.0000	--	--
	12 Weeks	172	5	0.9718	0.9335	0.9881
	24 Weeks	153	8	0.9548	0.9117	0.9771
Controls	0 Weeks	194	0	1.0000	--	--
	12 Weeks	181	9	0.9527	0.9110	0.9751
	24 Weeks	148	19	0.8982	0.8450	0.9338
Log-rank P= 0.0419 (2-sided)						

Program: Safety Survival Analyses.sas

Similar to findings in the FIX-HF-5C study on its own, $DAOOH_{HF}$ was significantly greater in the CCM Active treatment group compared with Controls during the 24-week (168 day) study period. For the CCM Treatment group, $DAOOH_{HF}$ averaged 165.8±16.1 in the Treatment group compared to 162.0±28.1 days in Controls (p=0.035), for an average difference of 3.9 days.

c. Summary of Kaplan-Meier Survival Analyses to Compare Freedom from Specific Events: Control vs. OPTIMIZER

There were no statistically significant differences between the active OPTIMIZER group and the control OMT group with respect to overall survival or freedom from cardiac death. Freedom from the composite of cardiac death and heart failure hospitalization was 7.9% higher in treatment compared to control (p=0.048 using Greenwood's formula for the variance) in the FIX-HF-5C population alone and was 5.7% higher in the combined FIX-HF-5 and FIX-HF-5C population (p=0.036 using Greenwood's formula for the variance and p=00419 by log-rank test). In the pooled population, patients experienced an overall 3.9 greater number of days alive out of the hospital for any reason, and the same number of more days alive not hospitalized for heart failure. Even in the FIX-HF-5C study alone CCM™ patients experienced a greater number of days alive not hospitalized for heart failure. Finally, the rates of cardiac and heart failure hospitalizations were significantly reduced in the FIX-HF-5C population (the population for which data were available) vs. the rates prior to implant.

1.4.6.17.2 Adverse Event Analyses

The final secondary safety endpoint in this study was an analysis of the incidence of serious adverse events observed during the 24-week study. All serious events reported have been adjudicated by the study's EAC. The EAC

was comprised of subject matter experts in cardiology. SAE narratives are provided in Attachment 11.

As summarized in Table 67 (for all subjects) and in Table 68, for the PP population, there were no statistically significant differences between the Control and OPTIMIZER groups for any serious adverse event tabulated.

Table 67: All Adverse Events and Adjudicated Serious Adverse Events by Treatment Group Occurring from Study Start to 24 Weeks (all subjects)

	All AE			Adjudicated Serious AE		
Event	**Optimizer x/n (%) (LCL, UCL) # Events**	**Control x/n (%) (LCL, UCL) # Events**	**P-value**	**Optimizer x/n (%) (LCL, UCL) # Events**	**Control x/n (%) (LCL, UCL) # Events**	**P-value (2-sided)**
All	35/74 (47.3) (35.6, 59.3) 73	36/86 (41.9) (31.3, 53.0) 61	0.5258	20/74 (27.0) (17.4, 38.6) 29	19/86 (22.1) (13.9, 32.3) 27	0.5800
Arrhythmia	4/74 (5.4) (1.5, 13.3) 4	5/86 (5.8) (1.9, 13.0) 5	1.0000	3/74 (4.1) (0.8, 11.4) 3	2/86 (2.3) (0.3, 8.1) 2	0.6631
Worsening Heart Failure	9/74 (12.2) (5.7, 21.8) 11	10/86 (11.6) (5.7, 20.3) 12	1.0000	3/74 (4.1) (0.8, 11.4) 4	7/86 (8.1) (3.3, 16.1) 8	0.3424
General Cardiopulmonary	7/74 (9.5) (3.9, 18.5) 9	6/86 (7.0) (2.6, 14.6) 6	0.5779	3/74 (4.1) (0.8, 11.4) 4	2/86 (2.3) (0.3, 8.1) 2	0.6631
Bleeding	2/74 (2.7) (0.3, 9.4) 2	1/86 (1.2) (0.0, 6.3) 1	0.5963	0/74 (0.0) (4.9, 0.0) 0	1/86 (1.2) (0.0, 6.3) 1	1.0000
Neurologic	1/74 (1.4) (0.0, 7.3) 1	0/86 (0.0) (4.2, 0.0) 0	0.4625	0/74 (0.0) (4.9, 0.0) 0	0/86 (0.0) (4.2, 0.0) 0	--
Thromboembolism	1/74 (1.4) (0.0, 7.3) 1	1/86 (1.2) (0.0, 6.3) 1	1.0000	1/74 (1.4) (0.0, 7.3) 1	1/86 (1.2) (0.0, 6.3) 1	1.0000
Local Infection	5/74 (6.8) (2.2, 15.1) 5	6/86 (7.0) (2.6, 14.6) 6	1.0000	1/74 (1.4) (0.0, 7.3) 1	4/86 (4.7) (1.3, 11.5) 4	0.3743
Sepsis	1/74 (1.4) (0.0, 7.3) 1	1/86 (1.2) (0.0, 6.3) 1	1.0000	1/74 (1.4) (0.0, 7.3) 1	1/86 (1.2) (0.0, 6.3) 1	1.0000
ICD/PM Malfunction	2/74 (2.7) (0.3, 9.4) 2	0/86 (0.0) (4.2, 0.0) 0	0.2123	2/74 (2.7) (0.3, 9.4) 2	0/86 (0.0) (4.2, 0.0) 0	0.2123
Optimizer Malfunction	8/74 (10.8) (4.8, 20.2) 9	--	--	6/74 (8.1) (3.0, 16.8) 6	--	--

	All AE			Adjudicated Serious AE		
Event	**Optimizer x/n (%) (LCL, UCL) # Events**	**Control x/n (%) (LCL, UCL) # Events**	**P-value**	**Optimizer x/n (%) (LCL, UCL) # Events**	**Control x/n (%) (LCL, UCL) # Events**	**P-value (2-sided)**
General Medical	18/74 (24.3) (15.1, 35.7) 28	17/86 (19.8) (12.0, 29.8) 29	0.5663	7/74 (9.5) (3.9, 18.5) 7	7/86 (8.1) (3.3, 16.1) 8	0.7864

Program: Safety Adverse Events.sas

Table 68: All Adverse Events and Adjudicated Serious Adverse Events by Treatment Group Occurring from Study Start to 24 Weeks (PP population)

	All AE			Adjudicated Serious AE		
Event	**Optimizer x/n (%) (LCL, UCL) # Events**	**Control x/n (%) (LCL, UCL) # Events**	**P-value**	**Optimizer x/n (%) (LCL, UCL) # Events**	**Control x/n (%) (LCL, UCL) # Events**	**P-value (2-sided)**
All	34/68 (45.9) (34.3, 57.9) 70	36/86 (41.9) (31.3, 53.0) 61	0.6342	19/68 (27.9) (17.7, 40.1) 28	19/86 (22.1) (13.9, 32.3) 27	0.4539
Arrhythmia	4/68 (5.4) (1.5, 13.3) 4	5/86 (5.8) (1.9, 13.0) 5	1.0000	3/68 (4.4) (0.9, 12.4) 3	2/86 (2.3) (0.3, 8.1) 2	0.6551
Worsening Heart Failure	8/68 (10.8) (4.8, 20.2) 10	10/86 (11.6) (5.7, 20.3) 12	1.0000	3/68 (4.4) (0.9, 12.4) 4	7/86 (8.1) (3.3, 16.1) 8	0.5138
General Cardiopulmonary	7/68 (9.5) (3.9, 18.5) 9	6/86 (7.0) (2.6, 14.6) 6	0.5779	3/68 (4.4) (0.9, 12.4) 4	2/86 (2.3) (0.3, 8.1) 2	0.6551
Bleeding	2/68 (2.7) (0.3, 9.4) 2	1/86 (1.2) (0.0, 6.3) 1	0.5963	0/68 (0.0) (0.0, 5.3) 0	1/86 (1.2) (0.0, 6.3) 1	1.0000
Neurologic	1/68 (1.4) (0.0, 7.3) 1	0/86 (0.0) (4.2, 0.0) 0	0.4625	0/68 (0.0) (0.0, 5.3) 0	0/86 (0.0) (0.0, 4.2) 0	--
Thromboembolism	1/68 (1.4) (0.0, 7.3) 1	1/86 (1.2) (0.0, 6.3) 1	1.0000	1/68 (1.5) (0.0, 7.9) 1	1/86 (1.2) (0.0, 6.3) 1	1.0000
Local Infection	5/68 (6.8) (2.2, 15.1) 5	6/86 (7.0) (2.6, 14.6) 6	1.0000	1/68 (1.5) (0.0, 7.9) 1	4/86 (4.7) (1.3, 11.5) 4	0.3842
Sepsis	1/68 (1.4) (0.0, 7.3) 1	1/86 (1.2) (0.0, 6.3) 1	1.0000	1/68 (1.5) (0.0, 7.9) 1	1/86 (1.2) (0.0, 6.3) 1	1.0000
ICD/PM Malfunction	2/68 (2.7) (0.3, 9.4) 2	0/86 (0.0) (4.2, 0.0) 0	0.2123	2/68 (2.9) (0.4, 10.2) 2	0/86 (0.0) (0.0, 4.2) 0	0.1934
Optimizer Malfunction	8/68 (10.8) (4.8, 20.2)	--	0.0017	6/68 (8.8) (3.3, 18.2)	--	--

	All AE			Adjudicated Serious AE		
Event	**Optimizer x/n (%) (LCL, UCL) # Events**	**Control x/n (%) (LCL, UCL) # Events**	**P-value**	**Optimizer x/n (%) (LCL, UCL) # Events**	**Control x/n (%) (LCL, UCL) # Events**	**P-value (2-sided)**
	9			6		
General Medical	17/68 (23.0) (14.0, 34.2) 26	17/86 (19.8) (12.0, 29.8) 29	0.6996	6/68 (8.8) (3.3, 18.2) 6	7/86 (8.1) (3.3, 16.1) 8	1.0000

Program: Safety Adverse Events PP.sas

The total number of adjudicated SAEs was 36. However only 29 occurred within the 24-week study period. Each of the 29 events are detailed below and a complete summary of each event has been provided in Attachment 11 –SAE Narratives

Table 69: Listing Serious Adverse Events / Primary Safety Events (OPTIMIZER Group Only)

Patient ID	Treated	Adverse Event Category/Description	Days to Onset	Device Related	Procedure Related	Complication (1° Safety Event)
06-402 PAS	Yes	OPTIMIZER generator reposition (protruding from pocket) with lead replacement	76	Definitely	Possibly	Y
06-404 RCW	No	General Medical - Hypertension	168	N	N	N
32-409 AMD	Yes	OPTIMIZER Lead dislodgement	80	Possibly	Definitely	Y
51-411 J-B	Yes	OPTIMIZER Lead dislodgement	0	N	Definitely	Y
51-420 KAS	Yes	Worsening Heart Failure - Dyspnea	49	N	N	N
51-420 KAS	Yes	General Medical - Abdominal Pain	59	N	N	N
51-420 KAS	Yes	Worsening Heart Failure - Dyspnea	89	N	N	N
51-426 SLS	Yes	OPTIMIZER Lead dislodgement	14	Possibly	Definitely	Y
51-456 WFC	Yes	General Cardiopulmonary - Myocardial Infarction	5	N	N	N
51-459 CDS	Yes	Deep Vein Thrombosis	8	Possibly	Definitely	Y
65-403 STP	Yes	General Medical - Esophagitis	151	N	N	N
65-445 GIC	Yes	Worsening Heart Failure - Dyspnea	64	N	N	N
65-445 GIC	Yes	General Cardiopulmonary - worsening coronary artery disease	102	N	N	N
65-471 SLC	Yes	OPTIMIZER Lead dislodgement	0	Possibly	Definitely	Y

Table 69: Listing Serious Adverse Events / Primary Safety Events (OPTIMIZER Group Only)

Patient ID	Treated	Adverse Event Category/Description	Days to Onset	Device Related	Procedure Related	Complication (1° Safety Event)
70-410 V-P	Yes	General Medical - choledocholithiasis	112	N	N	N
75-416 DDD	Yes	General Cardiopulmonary - Angina	79	N	N	N
75-416 DDD	Yes	General Medical - hypoglycemia	116	N	N	N
75-416 DDD	Yes	General Cardiopulmonary - Worsening CAD	127	N	N	N
79-402 BBB	Yes	Inappropriate ICD fire due to ICD lead failure	6	N	N	N
88-402 SET	Yes	General Medical - Sigmoid stricture with incarcerated hernia	144	N	N	N
88-402 SET	Yes	Localized Infection - Pneumonia	147	N	N	N
88-402 SET	Yes	Sepsis	161	N	N	N
90-413 G-G	Yes	Atrial flutter	162	N	N	N
90-424 H-F	Yes	ICD lead fracture	52	N	N	N
90-424 H-F	Yes	General Medical - Mood Disorder Psychosis	168	N	N	N
90-428 T-K	Yes	Worsening Heart Failure - Dyspnea	45	N	N	N
90-442 GSG	Yes	Atrial fibrillation	12	N	N	N
90-451 CLC	Yes	OPTIMIZER Lead dislodgement	2	Possibly	Definitely	Y
90-451 CLC	Yes	Brady Arrhythmia – Junctional Rhythm	9	N	N	N

Program: SAE Listing.sas

a. OPTIMIZER Malfunction

Per the case report form reporting instructions, an adverse event category called "OPTIMIZER Malfunction" is reported for any of the following occurrences:

- OPTIMIZER lead dislodgement
- OPTIMIZER lead fracture
- OPTIMIZER pulse generator
- OPTIMIZER sensing defect
- Other- To be specified

There were 6 events classified as an "OPTIMIZER Malfunction" reported during the 24-week study occurring in 6 subjects. Five (5) of the six events

were lead dislodgements and 1 was a lead extraction/replacement with a pocket revision due to increasing pain and discomfort at the IPG suture line with prominent exposure of the lead. None of these events were as a result of product quality issues or failures.

b. ICD/Pacemaker Malfunction

There were 2 ICD/Pacemaker malfunctions in the OPTIMIZER group. One incident was an ICD/ lead dislodgment. The other incident was an inappropriate firing of the ICD; testing at the time of the incident proved it was not due to crosstalk between the ICD and OPTIMIZER devices. There were no ICD/Pacemaker related SAEs in the Control group.

c. Arrhythmias

There were 5 serious AEs classified as an arrhythmia; 3 occurred in the OPTIMIZER group and 2 occurred in the Control group.

Table 70: Adjudicated Serious Adverse Events

Adjudicated Serious AE		
OPTIMIZER x/n (%) (LCL, UCL) # Events	**Control x/n (%) (LCL, UCL) # Events**	**P-value (2-sided)**
3/74 (4.1) (0.8, 11.4) 3	2/86 (2.3) (0.3, 8.1) 2	0.6631

Program: SAE Listing.sas

The following details the 3 arrhythmia SAEs in the OPTIMIZER group:

- Sixty-nine (69) year old female (Subject 90-413) with idiopathic cardiomyopathy and ICD (2011). The subject was randomized to the OPTIMIZER group on September 1, 2016 and was successfully implanted on September 10, 2016. The subject presented to the ER on February 19, 2017 (AE3- Arrhythmia: Atrial fibrillation) and was found to be in atrial flutter with a heart rate of 130 bpm. The subject remained in the hospital and underwent an ablation on February 22nd and was discharged on February 23rd. The AE was adjudicated and classified as "Not a Complication." The SAE was also re-categorized as "Arrhythmia: Atrial flutter" by the adjudication committee.

- Seventy (70) year old male (Subject 90-442) with idiopathic cardiomyopathy, a history of atrial fibrillation and ventricular tachycardia, and a dual-chamber ICD. The subject was randomized to the OPTIMIZER group on December 15, 2016 and was successfully implanted on December 17, 2016. When the subject was seen for the 2-week follow-up visit on December 29, 2016 (AE1- Atrial fibrillation), he was in atrial fibrillation. The subject's Eliquis dose was

increased with a plan to initiate Sotalol in 3 weeks. The subject underwent a successful cardioversion under sedation on January 27, 2017. The AE was adjudicated and classified as "Not a Complication."

- Eighty-two (82) year old male (Subject 90-451) with ischemic cardiomyopathy, CABG (2001) and a history of atrial fibrillation. The subject was randomized to the OPTIMIZER group on February 16, 2017 and was implanted on March 4, 2017. The subject developed evidence of sick sinus syndrome with SOB, dizziness and lightheadedness, and a long first-degree AV-block. On March 13, 2017 (AE1- Junctional rhythm) the Investigator decided the subject required a pacemaker and a dual-chamber pacemaker was implanted on March 17, 2017. The AE was adjudicated and classified as "Not a Complication."

None of the 3 events were reported as device related.

The following details the 2 arrhythmia SAEs in the Control group:

- Fifty-one (51) year old male (Subject 09-407) with idiopathic cardiomyopathy, MI on July 17, 2015, frequent PVCs, and a history of atrial fibrillation, which was well managed on amiodarone but medication was discontinued due to concern about side effects. The subject had previously declined an ICD implant due to his employment as a truck driver. The subject was randomized to the Control group on December 9, 2015 with a study start date (SSD) of January 11, 2016. On May 4, 2016 (AE2- Atrial Fibrillation) recurrent, persistent, symptomatic atrial fibrillation was reported. On May 13, 2016, he was admitted for a same day TEE cardioversion and discharged in normal sinus rhythm. This event was adjudicated and classified as "Not a Complication".
- Sixty-one (61) year old male (Subject 65-422) with ischemic cardiomyopathy, MI and PTCA (November 1, 2006), a history of atrial fibrillation and ventricular tachycardia, and a dual-chamber ICD implant (2013). The subject was randomized to the Control group on December 9, 2015 with a study start date of January 11, 2016. The subject had been experiencing palpitations and presyncope related to sustained ventricular tachycardia requiring multiple bursts of ATP from his defibrillator and was scheduled for catheter ablation. Sotalol was prescribed on February 28th pending the ablation. On March 21, 2016 (AE2-Sustained Ventricular Tachycardia) the subject was admitted for an ablation procedure. An Impella device was placed for temporary ventricular support during the procedure; mapping and the extensive ablation procedure took several hours and the subject was transferred to recovery in the ICU. This event was adjudicated and classified as "Not a Complication". The SAE onset date was reported as March 21, 2016 by the EAC instead of the site reported date of January 2, 2016.

d. Infection/Sepsis

There were 5 local infection serious AEs reported; 1 reported in the OPTIMIZER group and 4 in the Control group. There were 2 reports of sepsis; 1 in each group.

Table 71: Local infection reported as serious adverse events

	Adjudicated Serious AE		
Event	**OPTIMIZER x/n (%) (LCL, UCL) # Events**	**Control x/n (%) (LCL, UCL) # Events**	**P-value (2-sided)**
Local Infection	1/74 (1.4) (0.0, 7.3) 1	4/86 (4.7) (1.3, 11.5) 4	0.3743
Sepsis	1/74 (1.4) (0.0, 7.3) 1	1/86 (1.2) (0.0, 6.3) 1	1.0000

Program: SAE Listing.sas

The following details the 1 report of infection and 1 report of sepsis in the OPTIMIZER group, both events occurred in the same subject:

Seventy-three (73) year old female (subject 88-402) with ischemic cardiomyopathy, MI (April 29, 2016), PTCA (May 1, 2016) and diabetes. The subject was randomized to the OPTIMIZER group on December 19, 2016 and the device was implanted on January 5, 2017. The subject presented to the hospital on May 29, 2017 (AE1- General Medical: Sigmoid stricture with incarcerated hernia) with nausea, diarrhea and vomiting. CT scan showed a distal sigmoid stricture and multiple ventral hernias. The subject underwent surgery on May 30th, which included lower ventral resection with loop ileostomy, lysis of adhesions, and hernia repair with biologic mesh. The subject was left intubated when they transferred her to the recovery room. The subject developed acute hypoxic and hypercapnic respiratory failure, secondary to pneumonia and was placed on Bi-PAP, O_2 and antibiotics (for pneumonia and post-surgical purposes). She was diagnosed on **June 1, 2017 (AE12-Localized Infection: Pneumonia)** with bilateral pneumonia with secondary acute hypoxic and hypercapnic respiratory failure. The subject was scheduled to move to a skilled nursing facility (SNF) but on June 9, 2017 the colostomy bag leaked into the surgical incision with some dehiscence and erythema. Antibiotics were continued and a wound VAC placed. With the wound VAC in place and the incision and abdominal pain improving, the subject was discharged to a SNF on June 12th. The AE was adjudicated and classified as "Not a Complication."

The subject was presented to the ER and was readmitted to the hospital on **June 15, 2017 (AE13-Sepsis)** with pain, redness and swelling around the ileostomy

tube. She was septic and hypertensive; IV antibiotics and analgesics were initiated. The AE was adjudicated and classified as "Not a Complication."

The following details the 4 reports of infection and 1 report of sepsis in the Control group:

1. Fifty-five (55) year old female (Subject 55-413) with ischemic cardiomyopathy, MI (2006), PTCA (2012) and a dual-chamber ICD implant (2007). The subject was randomized to the Control group on August 24, 2015 with a study start date of September 10, 2015. The subject began experiencing symptoms of worsening dysuria on **September 16, 2015 (AE3-General Medical - UTI)** and presented to the ER and admitted to the hospital on September 20, 2015. She developed fever, rigors, nausea, vomiting, and myalgia; tested positive for urinary tract infection and pyelonephritis. Antibiotics, IV hydration, analgesic and antiemetics were administered. A cystoscopy was performed with a double J stent placed on September 22, 2015. Pyridium was provided for dysuria and bladder spasms. Symptoms improved and the subject was discharged on September 26th.

2. Sixty-two (62) year old female (Subject 56-402) with idiopathic cardiomyopathy, diabetes, hypertension, and hyperlipidemia. The subject was randomized to the Control group on April 23, 2015 with a study start date of May 13, 2015. On **May 21, 2015 (AE2- Sepsis: UTI)** the subject presented to the ER with symptoms of generalized weakness; admitted with urinary tract infection, sepsis, hypertension, and acute renal failure. Treated with IV Rocephin and IV fluids and discharged home in good condition; the antibiotic was transitioned to cephalexin. The subject's blood pressure, renal failure and sepsis improved and the patient was discharged on May 26, 2015.

3. Seventy-two (71) year old male (Subject 70-426) with idiopathic cardiomyopathy, diabetes, and a single-chamber ICD implanted on April 20, 2016. The subject was randomized to the Control group on September 19, 2016 with a study start date of September 29, 2016. The subject was admitted to the hospital on **January 4, 2017 (AE2- Localized Infection: Pneumonia)** and treated with IV diuretics and antibiotics and discharged on January 11, 2017.

4. Sixty (60) year old male (Subject 90-408) with idiopathic cardiomyopathy, diabetes, a history of atrial flutter and an ICD implanted on April 16, 2016. The subject was randomized to the **Control group** on August 17, 2016 with a study start date of August 20, 2016. As of **October 28, 2016 (AE1 – Localized Infection: Diabetic foot ulcer)** the subject developed a diabetic foot ulcer that was drained and beaded on November 28, 2016.

5. Fifty-one (51) year old male (Subject 90-435) with idiopathic cardiomyopathy, diabetes, a history of atrial fibrillation, and a dual-chamber

ICD (April 26, 2016). The subject was randomized to the Control group on October 26, 2016 and with a study start date of November 12, 2016. The subject was hospitalized on January 12, 2017 for chest pain and shortness of breath. IV Lasix, Losartan and amiodarone were prescribed. While there, he developed pneumonia **(January 22, 2017, AE7-Localized infection: Pneumonia)** and was treated with antibiotics. The admission was further complicated with renal failure and the subject was put on dialysis on January 30. The subject was discharged on February 2, 2017.

There was one additional adjudicated serious adverse event (worsening of heart failure) not reported in the table above. When the adjudication committee reviewed the event, they classified it as non-serious. Since this is the only non-serious adverse event, a separate table of non-serious events is not presented.

1.4.6.18 Summary of Safety Endpoints

The primary safety endpoint for the FIX-HF-5C study was met since the proportion of patients who were complication free exceeded 70% in the ITT population.

There were no statistically significant differences between the active OPTIMIZER group and the control OMT group with respect to overall survival or freedom from cardiac death. Freedom from the composite of cardiovascular death and heart failure hospitalization was 7.9% higher in treatment compared to control (p=0.048 using Greenwood's formula for the variance) in the FIX-HF-5C population alone and was 5.7% higher in the combined FIX-HF-5 and FIX-HF-5C population (p=0.036 using Greenwood's formula for the variance and p=0.0419 by log-rank test). In the pooled population, patients experienced an overall 3.9 greater number of days alive out of the hospital for any reason, and the same number of more days alive not hospitalized for heart failure. Even in the FIX-HF-5C study alone CCM patients experienced a greater number of days alive not hospitalized for heart failure. Finally, the rates of cardiac and heart failure hospitalizations were significantly reduced in the FIX-HF-5C population (the population for which data were available) vs. the rates prior to implant.

The incidence of adverse events in this study was in general relatively low. Comparisons between the treatment groups did not show any statistical differences between Control and OPTIMIZER groups with respect to any adverse event tabulated for the analysis. The data presented here allows us to conclude that the OPTIMIZER IVs, and therefore the OPTIMIZER SMART 3-Lead configuration by association, is safe for use in the population of patients with moderate-to-severe heart failure.

1.4.6.19 Exploratory Analyses

1.4.6.19.1 Evaluation of the primary effectiveness endpoint in the per protocol population

This Bayesian analysis is contained in the Primary & Key Secondary Analyses Impulse Dynamics FIX-HF-5C Report (Attachment 07).

1.4.6.19.2 Comparison of Peak VO_2 by Heart Failure Etiology (complete case analysis)

The unadjusted mean change from baseline at 24 weeks is presented in the table below by heart failure etiology. Significant treatment effects are seen in both groups.

Table 72: Unadjusted Mean Changes from Baseline in Peak VO_2 Scores at 24 Weeks (complete case analysis)

	Ischemic Etiology Mean (SD) N Med (Min, Max)		P-value[1]	Non-Ischemic Etiology Mean (SD) N Med (Min, Max)		P-value[1] (1-sided)
Study	**OPTIMIZER**	**Control**		**OPTIMIZER**	**Control**	
FIX-HF-5C	0.34 (2.69) 40 0.28 (-4.75, 5.9)	-0.31 (2.69) 41 -0.55 (-6.85, 4.9)	0.1429	-0.58 (2.79) 26 -0.1 (-7.3, 4.45)	-0.77 (1.81) 29 -1.2 (-4.4, 2.75)	0.2447
FIX-HF-5	-0.08 (2.78) 72 -0.2 (-6.6, 8.1)	-0.97 (2.39) 57 -1 (-6.4, 4.2)	0.0450	1.36 (3.48) 27 0.8 (-4.8, 11.7)	-1.05 (2.66) 32 -0.8 (-6.6, 6)	0.0037
Pooled	0.07 (2.74) 112 0 (-6.6, 8.1)	-0.7 (2.53) 98 -0.9 (-6.85, 4.9)	0.0293	0.41 (3.28) 53 0.3 (-7.3, 11.7)	-0.92 (2.28) 61 -0.8 (-6.6, 6)	0.0063

Program: Additional Exploratory.sas

[1]Two-sample Wilcoxon (one-sided) for difference between treatment groups.

The primary model of the completed cases data was refit separately by etiology. In addition, a term for etiology and the interaction between treatment groups and etiology was included in the primary model to examine the overall interaction between etiology and treatment effect.

Table 73: Least Squares Means from Repeated Measures Analysis of Variance for Peak VO_2 over Study Visits by Heart Failure Etiology (complete case analysis)

		Ischemic Etiology		Non-Ischemic Etiology		
Study	**Visit**	**Treatment Difference (LCL, UCL)**	**P-value[1]**	**Treatment Difference (LCL, UCL)**	**P-value[1]**	**Interaction P-value[2]**
FIX-HF-5C	12 Weeks	0.670 (-0.224, 1.564)	0.0704	-0.012 (-1.076, 1.053)	0.5080	0.5979
	24 Weeks	0.601 (-0.298, 1.500)	0.0944	0.247 (-0.818, 1.312)	0.3232	0.3415
FIX-HF-5	12 Weeks	-0.186 (-0.959, 0.588)	0.6806	1.440 (0.133, 2.746)	0.0156	0.3182
	24 Weeks	0.653 (-0.138, 1.444)	0.0522	2.377 (1.059, 3.695)	0.0003	0.3369
Pooled	12 Weeks	0.113 (-0.476, 0.702)	0.3521	0.759 (-0.102, 1.620)	0.0416	0.3205
	24 Weeks	0.599 (0.001, 1.197)	0.0247	1.336 (0.472, 2.201)	0.0013	0.2470

Program: Additional Exploratory.sas

[1] One sided P-value for difference in least squares means from mixed model by Etiology.
[2] Two sided for interaction between treatment and etiology from mixed model containing a main effect for etiology and visit by treatment by Etiology interaction.

While there are trends in differences in treatment effects by etiology, there is not a significant interaction between etiology and treatment effect at any time point for either study or for pooled studies. Thus, we can conclude that there is not a difference in treatment effects based on etiology. The overall conclusions by etiology remain consistent.

1.4.6.19.3 Comparison of Peak VO_2 for Subjects with Baseline EF ≥ 35

This analysis is contained in the Statistical Analysis Report of Impulse Dynamics FIX-HF-5C Study (Attachment 03).

1.4.6.19.4 Comparison of Peak VO_2 by Baseline NYHA Class (complete case analysis)

The unadjusted mean change from baseline at 24 weeks is presented in the table below.

Table 74: Unadjusted Mean Changes from Baseline in Peak VO_2 Scores at 24 Weeks (complete case analysis)

	NYHA III Mean (SD) N Med (Min, Max)		P-value[1]	NYHA IV Mean (SD) N Med (Min, Max)		P-value[1]
Study	**OPTIMIZER**	**Control**		**OPTIMIZER**	**Control**	
FIX-HF-C	0.2 (2.61) 56 0.33 (-7.3, 5.9)	-0.51 (2.33) 63 -0.55 (-6.85, 4.9)	0.0345	-1.29 (3.28) 10 -1.75 (-5.7, 3.95)	-0.41 (2.8) 7 -1.2 (-4.15, 4.15)	0.2321
FIX-HF	0.34 (3.11) 94 0.05 (-6.6, 11.7)	-0.97 (2.31) 76 -0.8 (-6.4, 4.2)	0.0040	-0.08 (1.19) 5 -0.2 (-1.2, 1.9)	-1.18 (3.37) 13 -1.3 (-6.6, 6)	0.1621
Pooled	0.29 (2.92) 150 0.2 (-7.3, 11.7)	-0.76 (2.32) 139 -0.8 (-6.85, 4.9)	0.0009	-0.89 (2.77) 15 -0.8 (-5.7, 3.95)	-0.92 (3.13) 20 -1.25 (-6.6, 6)	0.4470

Program: Additional Exploratory.sas

[1]Two-sample Wilcoxon (one-sided) for difference between treatment groups.

Next, the primary model applied to completed cases data was refit separately by etiology. In addition, a term for etiology and the interaction between treatment group and etiology was included in the primary model to examine the overall interaction between etiology and treatment effect.

Table 75: Least Squares Means from Repeated Measures Analysis of Variance for Peak VO2 over Study Visits by Heart Failure Etiology (complete case analysis)

		NYHA III		NYHA IV		
Study	**Visit**	**Treatment Difference (LCL, UCL)**	**P-value[1]**	**Treatment Difference (LCL, UCL)**	**P-value[1]**	**Interaction P-value[2]**
FIX-HF-C	**12 Weeks**	0.509 (-0.203, 1.221)	0.0799	-0.066 (-2.481, 2.349)	0.5237	0.9154
	24 Weeks	0.719 (0.004, 1.434)	0.0244	-0.956 (-3.37, 1.459)	0.7878	0.7090
FIX-HF	**12 Weeks**	0.15 (-0.562, 0.861)	0.3410	0.203 (-2.268, 2.675)	0.4330	0.2786
	24 Weeks	0.998 (0.275, 1.722)	0.0035	1.564 (-1.045, 4.173)	0.1156	0.4838
Pooled	**12 Weeks**	0.288 (-0.223, 0.799)	0.1337	0.265 (-1.343, 1.873)	0.3712	0.3138
	24 Weeks	0.871 (0.354, 1.388)	0.0005	0.239 (-1.393, 1.871)	0.3864	0.6519

Program: Additional Exploratory.sas

[1] One sided P-value for difference in least squares means from mixed model by Etiology.
[2] Two sided for interaction between treatment and etiology from mixed model containing a main effect for etiology and visit by treatment by Etiology interaction.

While there are trends for differences in treatment effects by baseline NYHA score, there is not a significant interaction between baseline NYHA score and treatment effect at any time point for either study or for the pooled studies. Thus, we can conclude that there is not a difference in treatment effects based on baseline NYHA score. The numbers with NYHA score equal 4 are small and thus interpretation of the results is difficult.

1.4.6.19.5 Comparison of Mean Changes from Baseline in the 6 Minute Walk

The unadjusted means and changes from baseline at 24 weeks in the 6-minute walk distances in meters are presented in the table below.

Table 76: Means and Mean Changes from Baseline in 6-Minute Walk Distance (m) at 24 Weeks (complete case analysis)

		Mean (SD) N Med (Min, Max)		P-value[1]
Study	**Visit**	**OPTIMIZER**	**Control**	
FIX-HF-5C	**Baseline**	316.85 (88.37) 74 308 (75, 462)	324.07 (89.71) 86 315 (120, 579)	0.8722
	24 Weeks	362.01 (100.6) 69 336 (170, 602)	332 (86.27) 72 324 (160, 552)	0.0981
	Change from Baseline to 24 Weeks	43.04 (80.73) 69 46 (-147, 350)	9.33 (87.43) 72 15.5 (-261, 152)	0.0234
FIX-HF-5	**Baseline**	325.8 (84.24) 117 321 (95, 525)	324.5 (91.64) 111 329 (120, 600)	0.9096
	24 Weeks	344.91 (99.17) 104 346 (90, 585)	333.73 (97.67) 91 340 (89, 644)	0.3415
	Change from Baseline to 24 Weeks	18.75 (82.49) 104 15.5 (-316, 225)	3.88 (80.19) 91 4 (-375, 255)	0.1976

		Mean (SD) N Med (Min, Max)		P-value[1]
Study	**Visit**	**OPTIMIZER**	**Control**	
Pooled	**Baseline**	322.34 (85.74) 191 320 (75, 525)	324.31 (90.57) 197 323 (120, 600)	0.9300
	24 Weeks	351.73 (99.81) 173 342 (90, 602)	332.96 (92.53) 163 336 (89, 644)	0.0808
	Change from Baseline to 24 Weeks	28.44 (82.43) 173 30 (-316, 350)	6.29 (83.25) 163 11 (-375, 255)	0.0120

Program: Additional Exploratory.sas

[1]Two-sample Wilcoxon (two-sided) for difference between treatment groups.

There is a statistically significant effect of treatment on the change in 6-minute walk distance at 24 weeks in the FIX-HF-C data (p=0.0234) and the combined pooled analysis (p=0.0120).

1.4.6.19.6 Comparison of Mean Changes from Baseline in the VE/VCO_2

The unadjusted means and changes from baseline at 24 weeks in VE/VCO_2 are presented in the table below.

Table 77: Means and Mean Changes from Baseline VE/VCO_2 at 24 Weeks (complete case analysis)

		Mean (SD) N Med (Min, Max)		P-value[1]
Study	**Visit**	**OPTIMIZER**	**Control**	
FIX-HF-C	**Baseline**	32.95 (5.43) 74 33 (22.5, 44)	34.15 (6.01) 86 33.5 (23.5, 56)	0.3190
	24 Weeks	33.87 (6.79) 68 33 (22.5, 54.5)	33.86 (6.32) 72 32 (25.5, 52)	0.9235
	Change from Baseline to 24 Weeks	1.07 (5.17) 68 0.75 (-11, 20)	0.39 (4.27) 72 -0.25 (-7.5, 17)	0.2595
FIX-HF	**Baseline**	34.3 (5.96) 117 33 (24, 59)	33.19 (6.31) 112 33 (19, 60)	0.1241
	24 Weeks	32.86 (6.48) 102 32 (-2, 56)	32.76 (6.44) 91 31 (21, 59)	0.4197
	Change from Baseline to 24 Weeks	-1.21 (5.94) 102 0 (-36, 10)	0.08 (4.35) 91 0 (-10, 13)	0.3369
Pooled	**Baseline**	33.78 (5.78) 191 33 (22.5, 59)	33.6 (6.18) 198 33 (19, 60)	0.6109
	24 Weeks	33.26 (6.6) 170 32.75 (-2, 56)	33.25 (6.39) 163 32 (21, 59)	0.5695
	Change from Baseline to 24 Weeks	-0.3 (5.74) 170 0 (-36, 20)	0.21 (4.3) 163 0 (-10, 17)	0.9001

Program: Additional Exploratory.sas

[1]Two-sample Wilcoxon (two-sided) for difference between treatment groups.

There were no significant effects of treatment on the change in VE/VCO_2 at 24 weeks in the FIX-HF-C data (p=0.2595), the FIX-HF-5 data (p=0.3369) or the combined pooled analysis (p=0.9001).

1.4.6.19.7 Comparison of Peak VO_2 and Primary Safety Endpoint by Gender

There were 7 primary safety endpoint complications that occurred in 4 males and 3 females. The following 2x2 contingency table, constructed for the 68 treated OPTIMIZER subjects, shows that the association between gender and the primary safety endpoint was not statistically significant:

Table 78: Comparison by Gender

	Males	Females	Total
Primary Safety Event	4 (8.2%)	3 (15.8%)	7
Event Free	45 (91.8%)	16 (84.2%)	61
Total	49	19	68
Fisher's Exact P-value = 0.39 (2-sided)			

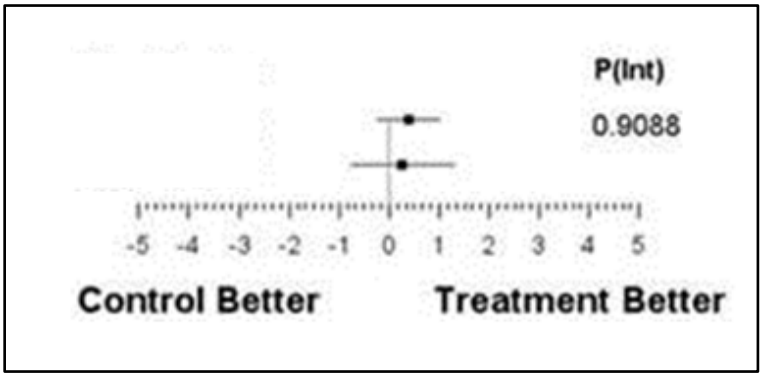
Program: Safety Primary by Gender.sas

The Forest plot below is for the primary efficacy endpoint (peak VO_2) with no imputation of data, with the differences at 24 weeks from the mixed model using all available data (complete case). P(int)=Interaction p-value for gender with treatment at 24 weeks.

Table 79: FIX-HF-5C Study Only

Group	Diff (95% CI)	P-Value (2-sided)
Male (N=121)	0.52 (-0.28, 1.32)	0.2046
Female (N=38)	0.36 (-0.97,1.69)	0.5927

Program: Primary Efficacy MalevFemale.sas



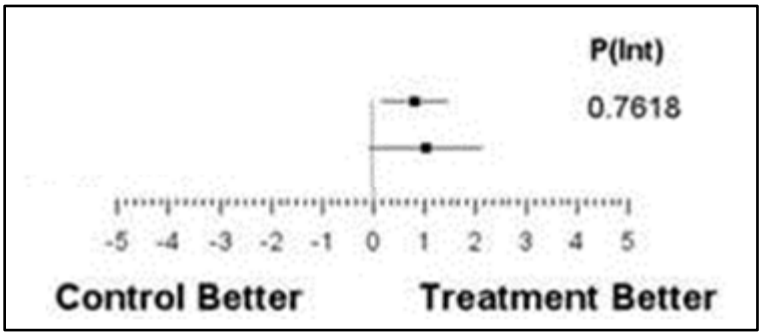
Program: F-Forest_Subgroup.sas
P-value: 2-sided

Figure 27: FIX-HF-5C Study Only

Table 80: FIX-HF-5 (subgroup) Study Only

Group	Diff (95% CI)	P-Value (2-sided)
Male (N=165)	1.04 (0.24, 1.83)	0.0109
Female (N=63)	1.30 (-0.06,2.66)	0.0605

Program: Primary Efficacy MalevFemale.sas



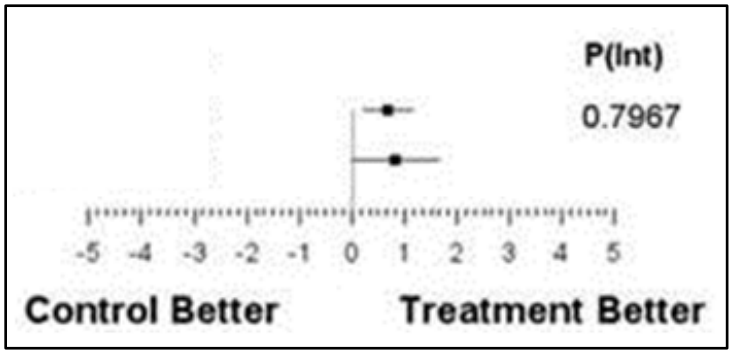
Program: F-Forest_Subgroup.sas
P-value: 2-sided

Figure 28: FIX-HF-5 (subgroup) Study Only

Table 81: FIX-HF-5 (subgroup) + FIX-HF-5C Pooled

Group	Diff (95% CI)	P-Value (2-sided)
Male (N=286)	0.80 (0.23, 1.37)	0.0059
Female (N=101)	0.97 (-0.02, 1.96)	0.0539

Program: Primary Efficacy MalevFemale.sas



Program: F-Forest_Subgroup.sas
P-value: 2-sided

Figure 29: FIX-HF-5 (subgroup) + FIX-HF-5C Pooled

1.4.6.19.8 Comparison of Peak VO2 in OPTIMIZER Subjects Implanted with Different Leads (FIX-HF-5C only)

There were 3 manufacturer's leads used in this study, St. Jude Medical (SJM), Biotronik, and BSC/Guidant. All but one subject had the same leads implanted in both locations. This subject had one SJM lead and one Biotronik lead. For the purposes of this analysis, this subject is analyzed in the Biotronik group. The analysis is repeated without this subject.

The unadjusted mean change from baseline at 24 weeks is presented in the table below for the three different leads.

Table 82: Unadjusted Mean Changes from Baseline in Peak VO_2 Scores at 24 Weeks (complete case analysis)

SJM (N=37) Mean (SD) N Med (Min, Max)	Biotronik (N=20) Mean (SD) N Med (Min, Max)	BSC/Guidant (N=11) Mean (SD) N Med (Min, Max)	P-value[1] (2-sided)
0.43 (2.23) 34 0.35 (-4.55, 5.90)	-1.04 (3.42) 19 -1.60 (-7.30, 5.50)	0.17 (2.90) 11 0.15 (-5.70, 3.650)	0.2344

Program: Additional Exploratory.sas

[1] K-sample Kruskal-Wallis Test.

Table 83: Unadjusted Mean Changes from Baseline in Peak VO_2 Scores at 24 Weeks removing the subject with two different leads (complete case analysis)

SJM (N=37) Mean (SD) N Med (Min, Max)	Biotronik (N=19) Mean (SD) N Med (Min, Max)	BSC/Guidant (N=11) Mean (SD) N Med (Min, Max)	P-value[1] (2-sided)
0.43 (2.23) 34 0.35 (-4.55, 5.90)	-1.01 (3.51) 18 -1.65 (-7.30, 5.50)	0.17 (2.90) 11 0.15 (-5.70, 3.650)	0.3046

Program: Additional Exploratory.sas

[1] K-sample Kruskal-Wallis Test.

The primary model on the complete case data was refit separately by lead type. All control subjects are used in each analysis, but the OPTIMIZER group is reduced to those in each lead category.

Table 84: Least Squares Means from Repeated Measures Analysis of Variance for Peak VO2 over Study Visits by Lead Type (complete case analysis)

	SJM		Biotronik		BSC/Guidant	
Visit	**Treatment Difference (LCL, UCL)**	**P-value[1]**	**Treatment Difference (LCL, UCL)**	**P-value[1]**	**Treatment Difference (LCL, UCL)**	**P-value[1]**
12 Weeks	0.426 (-0.363, 1.214)	0.1452	0.097 (-0.923, 1.116)	0.4248	0.947 (-0.319, 2.213)	0.0704
24 Weeks	0.930 (0.141, 1.719)	0.0107	-0.446 (-1.482, 0.591)	0.8018	0.546 (-0.72, 1.812)	0.1983

Program: Additional Exploratory.sas

1 One sided P-value for difference in least squares means from mixed model by Lead type.

Table 85: Least Squares Means from Repeated Measures Analysis of Variance for Peak VO_2 over Study Visits by Lead Type removing the subject with two different leads (complete case analysis)

	SJM		Biotronik		BSC/Guidant	
Visit	**Treatment Difference (LCL, UCL)**	**P-value[1]**	**Treatment Difference (LCL, UCL)**	**P-value[1]**	**Treatment Difference (LCL, UCL)**	**P-value[1]**
12 Weeks	0.426 (-0.363, 1.214)	0.1452	0.004 (-1.039, 1.047)	0.4960	0.947 (-0.319, 2.213)	0.0704
24 Weeks	0.930 (0.141, 1.719)	0.0107	-0.427 (-1.488, 0.635)	0.7847	0.546 (-0.72, 1.812)	0.1983

Program: Additional Exploratory.sas

[1] One sided P-value for difference in least squares means from mixed model by Lead type.

While there are some observed differences in treatment effects by Lead type, there is not a significant difference between the lead types in terms of change in Peak VO_2 at 24 weeks.

1.4.6.19.9 Comparison of Hospitalizations in patients with EF<35% versus EF≥35%

As detailed in the *Primary Analysis & Key Secondary Analysis Report* (Attachment 07), the impact of CCM™ on exercise tolerance and quality of life indices was significantly greater in patients with EF≥35%, though still clinically and statistically significant in patients with EF<35%. It was also shown that compared to Controls, patients treated with CCM™ had better survival free of heart failure hospitalizations and greater total number of days alive out of hospital during the study period. It was also explored whether the impact of CCM™ on heart failure hospitalizations differed by LVEF. Results are summarized in Tables 86, 87 and 88 for patients in the FIX-HF-5C population, the FIX-HF-5 populations and in the pooled populations.

In the FIX-HF-5C study alone (Table 86), the rate of survival and survival free of the composite of death and hospitalizations was very high in patients with EF≥35% and did not differ between Treatment and Control. In patients with EF<35%, survival free of the composite of cardiovascular death and heart failure hospitalizations trended for CCM™ between (0.97 vs 0.87, p=0.077) as were survival free of cardiac death (1.0 vs 0.95, p=0.14) and survival free of heart failure hospitalizations (0.97 vs 0.90, p=0.18). Similar trends were observed in the FIX-HF-5 study as well (Table 87). Thus, in the FIX-HF-5C and FIX-HF-5 pooled population (Table 88), survival free of cardiovascular death and heart failure hospitalizations was significantly improved by CCM™ (0.97 vs 0.88, p=0.009), an effect that was driven primarily by improved survival free of heart failure hospitalizations (0.97 vs 90.0, p= 0.032). CV deaths were also trending in favor of reduced events in the treatment group. Even though event rates were low in the EF≥35% group, there was no indications of any adverse effects.

Table 86: FIX-HF-5C only

Treatment Group	Time	Number at Risk	Total Number Failed	Proportion Surviving	Lower 95% CI	Upper 95% CI	Log-Rank P	Number at Risk	Total Number Failed	Proportion Surviving	Lower 95% CI	Upper 95% CI	Log-Rank P
		EF < 35						EF ≥ 35					
Cardiac Death and HF Hospitalizations													
Active	0 Weeks	39	0	1	.	.	0.0774	29	0	1	.	.	0.5908
	12 Weeks	38	1	0.9744	0.8316	0.9963	.	28	1	0.9655	0.7795	0.9951	.
	24 Weeks	31	1	0.9744	0.8316	0.9963	.	19	1	0.9655	0.7795	0.9951	.
Controls	0 Weeks	54	0	1	.	.	.	30	0	1	.	.	.
	12 Weeks	47	6	0.8889	0.7693	0.9485	.	29	1	0.9667	0.7861	0.9952	.
	24 Weeks	26	7	0.8687	0.744	0.9352	.	17	2	0.9333	0.7589	0.9829	.
Cardiac Death													
Active	0 Weeks	39	0	1	.	.	0.1422	29	0	1	.	.	.
	12 Weeks	39	0	1	.	.	.	29	0	1	.	.	.
	24 Weeks	34	0	1	.	.	.	20	0	1	.	.	.
Controls	0 Weeks	56	0	1	.	.	.	30	0	1	.	.	.
	12 Weeks	51	3	0.9458	0.8412	0.9822	.	30	0	1	.	.	.
	24 Weeks	39	3	0.9458	0.8412	0.9822	.	23	0	1	.	.	.
HF Hospitalizations													
Active	0 Weeks	39	0	1	.	.	0.1824	29	0	1	.	.	0.5908
	12 Weeks	38	1	0.9744	0.8316	0.9963	.	28	1	0.9655	0.7795	0.9951	.
	24 Weeks	31	1	0.9744	0.8316	0.9963	.	19	1	0.9655	0.7795	0.9951	.
Controls	0 Weeks	54	0	1	.	.	.	30	0	1	.	.	.
	12 Weeks	47	4	0.9245	0.8113	0.971	.	29	1	0.9667	0.7861	0.9952	.
	24 Weeks	26	5	0.9035	0.7833	0.9587	.	17	2	0.9333	0.7589	0.9829	.

Program: Safety Survival Analyses.sas
P-value: 2-sided

Table 87: FIX-HF-5 only

Treatment Group	Time	Number at Risk	Total Number Failed	Proportion Surviving	Lower 95% CI	Upper 95% CI	Log-Rank P	Number at Risk	Total Number Failed	Proportion Surviving	Lower 95% CI	Upper 95% CI	Log-Rank P
		EF < 35						EF ≥ 35					
Cardiac Death and HF Hospitalizations													
Active	0 Weeks	91	0	1	.	.	0.0625	18	0	1	.	.	0.2774
	12 Weeks	89	2	0.978	0.915	0.9945	.	17	1	0.9444	0.6664	0.992	.
	24 Weeks	88	3	0.967	0.9013	0.9892	.	15	3	0.8333	0.5677	0.943	.
Controls	0 Weeks	88	0	1	.	.	.	19	0	1	.	.	.
	12 Weeks	84	2	0.977	0.9112	0.9942	.	19	0	1	.	.	.
	24 Weeks	76	9	0.8946	0.8072	0.9437	.	18	1	0.9474	0.6812	0.9924	.
Cardiac Death													
Active	0 Weeks	91	0	1	.	.	0.9778	18	0	1	.	.	0.1405
	12 Weeks	90	1	0.989	0.9246	0.9984	.	17	1	0.9444	0.6664	0.992	.
	24 Weeks	90	1	0.989	0.9246	0.9984	.	16	2	0.8889	0.6242	0.971	.
Controls	0 Weeks	88	0	1	.	.	.	19	0	1	.	.	.
	12 Weeks	85	1	0.9885	0.9212	0.9984	.	19	0	1	.	.	.
	24 Weeks	84	1	0.9885	0.9212	0.9984	.	19	0	1	.	.	.
HF Hospitalizations													
Active	0 Weeks	91	0	1	.	.	0.1012	18	0	1	.	.	0.9354
	12 Weeks	89	2	0.978	0.915	0.9945	.	17	0	1	.	.	.
	24 Weeks	88	3	0.967	0.9013	0.9892	.	15	1	0.9375	0.6323	0.991	.
Controls	0 Weeks	88	0	1	.	.	.	19	0	1	.	.	.
	12 Weeks	84	1	0.9885	0.9212	0.9984	.	19	0	1	.	.	.
	24 Weeks	76	8	0.9051	0.8192	0.9514	.	18	1	0.9474	0.6812	0.9924	.

Program: Safety Survival Analyses.sas
P-value: 2-sided

Table 88: FIX-HF-5 and FIX-HF-5C Pooled

Treatment Group	Time	Number at Risk	Total Number Failed	Proportion Surviving	Lower 95% CI	Upper 95% CI	Log-Rank P	Number at Risk	Total Number Failed	Proportion Surviving	Lower 95% CI	Upper 95% CI	Log-Rank P
		EF < 35						EF ≥ 35					
Cardiac Death and HF Hospitalizations													
Active	0 Weeks	130	0	1	.	.	0.0087	47	0	1	.	.	0.6549
	12 Weeks	127	3	0.9769	0.9302	0.9925	.	45	2	0.9574	0.8404	0.9892	.
	24 Weeks	119	4	0.9692	0.9201	0.9883	.	34	4	0.9149	0.7889	0.9672	.
Controls	0 Weeks	142	0	1	.	.	.	49	0	1	.	.	.
	12 Weeks	131	8	0.9434	0.8899	0.9713	.	48	1	0.9796	0.8638	0.9971	.
	24 Weeks	102	16	0.8836	0.817	0.9271	.	35	3	0.9388	0.8221	0.9798	.
Cardiac Death													
Active	0 Weeks	130	0	1	.	.	0.2115	47	0	1	.	.	0.1466
	12 Weeks	129	1	0.9923	0.9467	0.9989	.	46	1	0.9787	0.8584	0.997	.
	24 Weeks	124	1	0.9923	0.9467	0.9989	.	36	2	0.9574	0.8404	0.9892	.
Controls	0 Weeks	144	0	1	.	.	.	49	0	1	.	.	.
	12 Weeks	136	4	0.9719	0.9269	0.9894	.	49	0	1	.	.	.
	24 Weeks	123	4	0.9719	0.9269	0.9894	.	42	0	1	.	.	.
HF Hospitalizations													
Active	0 Weeks	130	0	1	.	.	0.032	47	0	1	.	.	0.7038
	12 Weeks	127	3	0.9769	0.9302	0.9925	.	45	1	0.9783	0.8555	0.9969	.
	24 Weeks	119	4	0.9692	0.9201	0.9883	.	34	2	0.956	0.8354	0.9888	.
Controls	0 Weeks	142	0	1	.	.	.	49	0	1	.	.	.
	12 Weeks	131	5	0.9643	0.9163	0.985	.	48	1	0.9796	0.8638	0.9971	.
	24 Weeks	102	13	0.9032	0.8391	0.9427	.	35	3	0.9388	0.8221	0.9798	

Program: Safety Survival Analyses.sas
P-value: 2-side

1.4.6.20 CCM™ Therapy Delivery During FIX-HF-5C Study

1.4.6.20.1 Dosage

Impulse Dynamics conducted multiple clinical trials which explored several therapy dosage timing configurations that were proven to provide a desirable clinical benefit. For example, the FIX-HF-3 study delivered CCM™ at a "dose" of 3 hours/day administered *continuously* for 3 hours once a day. In the FIX-3-ext and FIX-CHF-4 studies, CCM™ was delivered in 1 hour intervals for a total of 7 hours/day, while in the FIX-HF-5 study, the CCM™ "dose" was reduced to 5 hours/day, also in 1-hour intervals equally spaced throughout the day. Of note, a single center study (FIX-CHF-13) did a preliminary evaluation of 5 vs. 12 hours/day therapy dosage which did not indicate a clinical difference between the two times.[18]

1.4.6.20.2 Number of Hours/Day

As the difference in clinical performance of 5 versus 12 hours/day was not found to be significant, the schedule recommended by Impulse Dynamics is 5 hours per day in equally-spaced 1-hour intervals. Dosage of CCM™ therapy, as delivered in the FIX-HF-5C trial, was pre-set at 5 hours duration in a given 24 hour period. The therapy delivery duration was non-programmable.

This "therapy delivery period" started each day at 00:00 hours and was delivered in increments lasting 1 hour in duration. After each one hour period, CCM signal delivery is halted for 3.8 hours. This cycle continued until 23:59 hours at which time the cycle repeats. This cycle continues unless interrupted by certain preprogrammed safety features, such as high PVC count, atrial arrhythmia, etc.

Table 89: CCM™ Therapy delivery cycle

CCM	Duration	Start Time	End Time
On	**1 hour**	**00:00 HRS**	**01:00 HRS**
Off	3 hours 48 minutes	01:01 HRS	04:48 HRS
On	**1 hour**	**04:49 HRS**	**05:48 HRS**
Off	3 hours 48 minutes	05:49 HRS	09:36 HRS
On	**1 hour**	**09:37 HRS**	**10:36 HRS**
Off	3 hours 48 minutes	10:37 HRS	14:24 HRS
On	**1 hour**	**14:25 HRS**	**15:24 HRS**
Off	3 hours 48 minutes	15:25 HRS	19:12 HRS
On	**1 hour**	**19:13 HRS**	**20:12 HRS**

CCM	Duration	Start Time	End Time
Off	3 hours 48 minutes	20:13 HRS	23:59 HRS

1.4.6.20.3 CCM™ Percentage per Day

Subjects have their Optimizer device interrogated at every study visit, during which CCM delivery percentage and other diagnostic data is gathered. Despite the 5 hours of scheduled CCM therapy, the programmed cycle may be interrupted when there is a high PVC count, atrial fibrillation, or any other type of tachyarrhythmia. The total amount of time CCM therapy is delivered can be estimated based on the number of CCM beats delivered (recorded as total trains). Assuming the average heart rate is 72bpm, approximately 21,600 CCM trains would equate to 5 hours (100%) of CCM effectively provided. During the FIX-HF-5C study, over 80% of the subjects received the full 5 hours and approximately 94% of the subjects received more than 80% of the CCM therapy. The remaining 6% of the subjects received less than 4 hours of therapy due primarily to a high number of PVCs or new onset atrial fibrillation.

Table 90: CCM™ Therapy Delivery Summary

Hours/day	% CCM	% of Subjects	Reasons for <5hr delivery
4.0 - 5.0	80-100%	94%	4 subjects with atrial fibrillation, 6 with a high PVC count, 2 with therapy delivery timing changes, all others with no explanation provided
0.00 – 3.9	0-79%	6%	6 subjects with high PVC count, 1 with atrial fibrillation, all others no explanation provided

1.4.6.20.4 CCM Delivery Programming

Impulse Dynamics discovered that electrical currents delivered during Phase 2 of the ventricular action potential lead to an increase in ventricular contractility. The actual CCM™ signal parameters were developed based on animal experiments, engineering considerations, and clinical experience.[19]

As described by Prutchi and Norris in "Design and Development of Medical Electronic Instrumentation,"[20] CCM™ signals consist of charge-balanced biphasic pulse bursts of 5 to 10 ms in duration per phase; one to three pulses per

burst delivered 30 to 60 ms into ventricular absolute refractory period.

CCM™ delivery must occur within the absolute refractory period. Programmability allows the physician to deliver the CCM™ signal at a time when it produces maximal effect on contractility. As shown in Figure 30, the delay and duration of the CCM™ pulse train were selected to place the CCM™ signal fully within the ventricular action potential's plateau (Phase 2), leaving sufficient margin of safety to stay clear of ventricular repolarization (T-wave). Biphasic pulses and a 40 ms balancing phase were chosen to ensure net-zero current flow to prevent electrochemical damage to the tissue. Lastly, CCM™ pulse phase durations in the 5-7 ms range were shown in animal experiments to yield the desired contractility-enhancement effects.

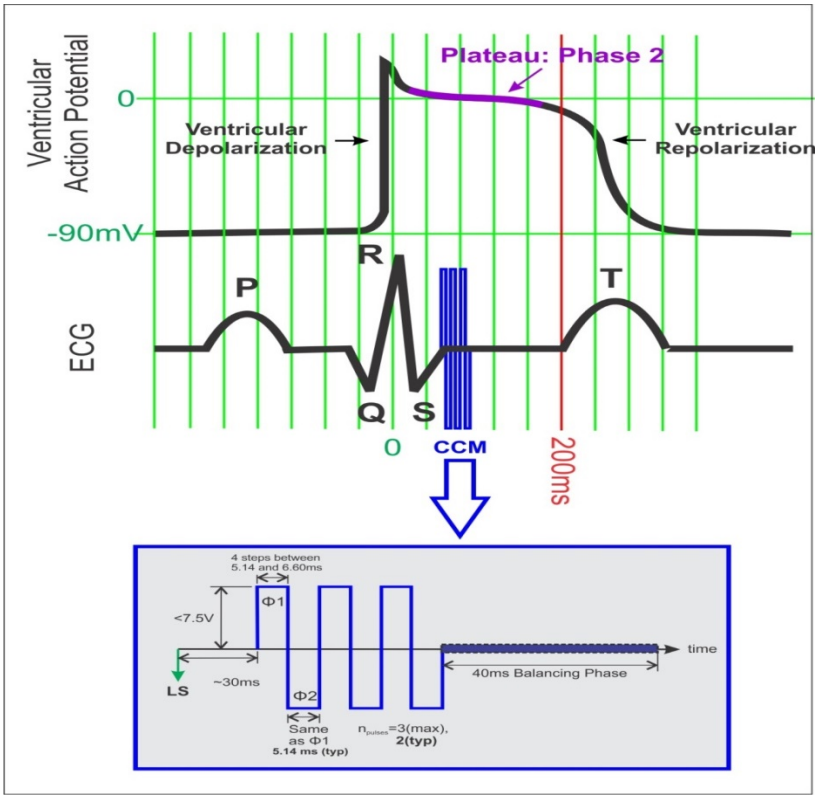


Figure 30: Delay and Duration of CCM™ Pulse Train

The start of the timing cycle for CCM™ signal delivery is triggered by the "Local Sense" event. The delay parameter (coupling interval) is the time interval between the leading edge of the Local Sense triggering event and the start of CCM™ pulse train delivery. With the OMNI II Programmer, the delay parameter can be set to values between 3 ms and 140 ms. To determine the proper programmed setting, the following criteria are applied:

- Programmed value is initiated by LS event
- Appropriate programmed value is 35ms after second sensed ventricular event, either the RV or LS event, *whichever occurs last*

- If LS event is after RV event, programmed value should be 35ms
- If RV event is after LS event, programmed value should be 35ms plus the measured RV-LS interval

Further descriptions of the CCM signal are provided in the following sections.

a. CCM Train Delay

The Train Delay is a programmable value between 3 and 140 ms in increments of 1 ms. The "Standard" or nominal setting is 35 ms. The purpose of this Train Delay is to ensure the entire ventricular mass (right and left) is depolarized. There is no specific value that would always be correct, since each patient's conduction system serves as their own norm.

b. Phase duration

The phase duration limits the amount of energy delivered to the patient in one event. The phase duration of the pulses comprising the CCM™ signal can be programmed with the OMNI II Programmer to one of 4 possible values between 5.14 ms and 6.60 ms. The duration of both phases is automatically set to identical values. At no time can they be programmed to different values. The nominal setting for this Phase Duration is 5.14 ms.

As described by Prutchi and Norris in "Design and Development of Medical Electronic Instrumentation,"[20] CCM™ signals consist of charge-balanced biphasic pulse burst of 5 to 10 ms in duration per phase; one to three pulses per burst delivered 30 to 60 ms into the ventricular absolute refractory period.

Biphasic pulses with phase duration of 5.14 to 6.60 ms delivered during the absolute refractory period of the heart have been shown to be therapeutic when treating patients with CHF. The effectiveness of these signals has been reported by Morita et al.[21]

Programmability of the Phase Duration allows the physician to modulate the intensity of the therapy: Patients with discomfort felt at the time of therapy delivery could be treated by increasing the phase duration. If no discomfort is felt at the initiation of therapy, the Phase Duration is left at the nominal setting.

1.5 Discussion

The results of this investigation confirm that CCM™ is safe and significantly improves exercise tolerance (peak VO_2), quality of life (MLWHFQ score), and functional status (NYHA class) in patients with heart failure and EF ranging from 25% to 45%, QRS duration <130 ms, normal sinus rhythm and persistent functional class NYHA III or ambulatory IV symptoms despite guideline directed medical therapies. These observations are further supported by a between-group difference (improvement) in 6MHW distance in excess of 30 meters favoring CCM™ Treatment over Control. Additional sensitivity analyses further confirmed the robustness of the findings, independent of other assumptions concerning the methods of Bayesian borrowing and imputation for deaths and missing data. Finally, a significant reduction in the composite of cardiac deaths and heart failure hospitalizations was observed.

An analysis of a small subset of the FIX-HF-5 study population (n=38) (further discussed in section 6.3 below) suggested that CCM™ treatment effects were particularly large in patients with EF ≥35%. That finding was also further corroborated when data from an additional 59 patients from the FIX-HF-5C study were included in the analysis. This cohort is of interest since these patients do not have an indication for an ICD, so that a standalone CCM™ device could be applicable.

In addition to the data of the present study, the safety of CCM™ has been consistently demonstrated in prior studies.[22,23,3] In particular, the FIX-HF-5 study demonstrated that 1-year event-free survival was noninferior in the CCM™ group compared to the Control group[22] Consistent across studies has been the finding that the rate and severity of overall adverse events is not significantly different than in the respective control group, despite the fact that the Control group does not receive a device implant.

The magnitude of the treatment effect of CCM™ on peak VO_2 is comparable to those identified in patients studied in prior studies of Cardiac resynchronization therapy (CRT). These include MIRACLE (0.9 ml/kg/min)[Error! Bookmark not defined.], MIRACLE-ICD (1.0 ml/kg/min)[Error! Bookmark not defined.], CONTAC-CD (0.8 ml/kg/min)[Error! Bookmark not defined.]. Although these studies have different entry criteria, they do provide a basis for comparing effects of CCM™ to CRT. The current study also identified a significant reduction of the composite of cardiovascular death and heart failure hospitalizations which are important therapeutic targets for this therapy.

While the current study was too short in duration and included too few patients to fully address survival benefit, prior studies have provided evidence of beneficial effects on survival and hospitalizations. The European registry (CCM-REG, fully discussed in section 5 below) provides further evidence of the impact and magnitude of CCM™ in reducing cardiac hospitalization.

CRT has long been available for patients with EF ≤35%, normal sinus rhythm, QRS duration ≥130 ms and persistent NYHA class III or ambulatory class IV symptoms despite guideline-directed medical therapies. However, HF patients not qualifying for CRT represent a large group suffering from poor quality of life and poor exercise tolerance despite optimal medical therapies. While ICDs are applicable to the broad population of patients with EF ≤35%, they

do not deliver a therapy for improving exercise tolerance or quality of life. It is noteworthy that for patients with EF <35%, a device that combines CCM and ICD functions is under development. Similarly, indwelling pulmonary artery pressure sensors are also applicable and help optimize medical therapies but do not, on their own, provide a heart failure therapy. Thus, there is a relatively large cohort of heart failure patients failing medical therapy that do not have the benefit of a simply implanted device-based therapy. It is such patients that CCM™ is currently designed to serve.

Conclusions

In summary, the results of the present study supplement and confirm results of prior studies in showing that CCM™ is safe and improves exercise tolerance and quality of life in patients with EF ranging from 25% to 45%, QRS duration <130 ms, normal sinus rhythm and persistent NYHA class III or ambulatory class IV symptoms despite guideline directed therapies including medications and ICDs when indicated. The composite of cardiovascular deaths and heart failure hospitalizations was reduced. The clinical effects were observed across the range of EFs studied, and clinical effectiveness was even greater in patients with EFs between 35 and 45% consistent with the FIX-HF-5 study.

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