Clinical Research Protocol

FIX-HF-5CA: Continued Access Protocol for the Evaluation of the OPTIMIZER Smart System in Subjects with Moderate-to-Severe Heart Failure with Ejection Fraction between 25% and 45%

Protocol ID CP OPT2017-004

ORIGINAL Version: March 5, 2017*

Revised April 3, 2017*
Revised April 7, 2017
Revised October 1, 2018*
Revised February 11, 2019**
Revised February 14, 2019
Revised March 27, 2019

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

** Site to Investigators but quickly retracked and replaced with February 14, 2019 version.

Sponsor: Impulse Dynamics (USA), Inc.
30 Ramland Road South, Suite 204
Orangeburg, New York 10962
Tel: 845-359-2389
Fax:845-818-3684

CONTENTS

I. BACKGROUND INFORMATION

Impulse Dynamics sponsored 4 studies under IDE # G030099, which was originally approved by the FDA on May 6, 2004. The protocols include the following:

1. FIX-HF-5 (Phase I and Phase II) Study
2. FIX-HF-5B/C Confirmatory Study
3. FIX-HF-5C2 (2-lead) Confirmatory Study
4. FIX-HF-5CA Continued Access Study (current protocol)

The PMA, including data from the first two studies, has been submitted to the FDA and is waiting for FDA determination. PMA approval would grant Impulse Dynamics permission to market the Optimizer 3-lead configuration of the device. The FIX-HF-5C2 (2-lead) Confirmatory Study completed enrollment and a PMA Supplement submission to the FDA is anticipated to occur around July of 2019. Continued Access to the 2-lead device in the FIX-HF-5CA study is expected to continue while the marketing application for the Optimizer 2-lead system is under review. Preliminary evidence shows that the Optimizer System with 2-leads is likely to be effective and no significant safety concerns have been identified for the proposed indication in patients with moderate to severe heart failure with an LVEF of 25-45% (inclusive).

A. Name and description of investigational device

The investigational device is the OPTIMIZER Smart System, a system capable of delivering non-excitatory cardiac contractility modulation signals. These electrical signals are intended to influence myocardial properties in patients with chronic heart failure. The System consists of three major components:

1. **OPTIMIZER Smart implantable pulse generator** (IPG), Model CCM X10; #2 torque wrench for securing the implanted leads
2. **OMNI Smart Programmer, model OMNI II** (with OMNI Smart Application Software), which interfaces with the IPG via a standard programming wand, providing the means to set system parameters and assess device diagnostics;
3. **OMNI Smart Charger** consisting of a charger unit and wand (Mini Charger);

B. Specified accessory leads

Two commercially available intravascular leads complete the system. They include two right ventricular leads to sense ventricular activation and deliver CCM signals. Both of these leads are bipolar leads approved for transvenous intracardiac ventricular pacing, have a standard IS-1 bipolar connector, active fixation with electrically-active corkscrew distal electrode with a minimal electrically-active surface area of 3.6 mm^2, and the distal electrode is coated with low-polarization coating (e.g., titanium nitride or iridium oxide).

- Biotronik Setrox lead
- Biotronik Solia S lead
- Boston Scientific Dextrus 4135, 4136 and 4137 lead
- St. Jude/Abbott Tendril DX 1688T, 1888 or 2088 active fixation lead
- Others as qualified by Impulse Dynamics and approved by FDA

C. Description of packaging and labeling

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

D. Summary of Prior Investigations

1. Bibliography of Publications

Pacemaker implantation has been well documented as the standard of care for treatment of certain types of cardiac rhythm disorders. The literature related to this therapy is voluminous and readily available. A bibliography of all publications relevant to CCM treatment 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 been used to inform the design of CCM signal application and are therefore relevant to the present investigation. Both devices are used in patients with symptomatic heart failure usually

together with ICDs. The symptomatic improvement with CCM is similar to that observed with CRT as reflected by comparisons in the literature. More recently it has been shown that CRT is not effective and may be detrimental in patients with QRS duration < 130ms, a niche group where CCM may have benefit.

2. 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 [Brunckhorst, 2006]. 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 contractility were associated with prolongation of the action potential, whereas signals that depressed contractility 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.

3. Acute animal studies

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.

CCM has also been tested in normal dogs in which left bundle branch block was induced, and compared with CRT [Nassir 2002]. CCM increased LV dP/dt and LVEF (increase of 15% points) significantly from baseline and more than that seen with CRT. CCM, CRT or CCM+CRT had no significant effect on diastolic function. CCM+CRT were no more effective than CCM alone.

4. 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 periods. The pulse generator turned on and off automatically for the intended periods when the device was activated.

The effects of CCM signals on gross and histologic appearance of the myocardium were indistinguishable from those observed with simulated pacing signals. At lead insertion sites,

mature fibrous material devoid of signs of acute inflammation was observed. There was no effect on histologic appearance of myocardium remote from the lead insertion sites.

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

CCM elicits chronic improvement in fetal gene expression and calcium handling pathway components in heart failure [Imai 2007]. When compared to control, 3 months of CCM treatment resulted in an increase in EF (27±1 – 33%±1), and reductions in LVESV and LVEDV as well as LVEDP (from 14±1 to 8±1). Remodeling was coincident with improvements in alpha-myosin heavy chain expression and levels of ANP, BNP, SERCA2, phospholamban, ryanodine receptor, and calsequestrin [Zhang 2016] showed improved structure in CHF treated with CCM in a 12 week aortic constriction rabbit model of heart failure. In this model, CCM reduced fibrosis and collagen levels in the heart tissue while downregulating MMP2, MMP-9, alpha-smooth muscle actin, and TGF-β1.

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 provides pre-clinical insight into long term safety of the system through testing CCM across a very wide range of myocardial function 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. It is unlikely that longer testing durations in animals would result in any different outcomes.

5. Summary of findings from completed U.S. IDE clinical protocols

FIX HF-5 (Phase I):Multicenter, randomized, double blind Feasibility Study

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.

FIX HF-5 (Phase II): Prospective, multicenter, randomized Pivotal Trial

The US Pivotal Trial (also referred to as the Phase II Study) was designed to evaluate the 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 years), 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 mlO_2/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%.

FIX HF-5C Confirmatory Study (US and Europe)

The Confirmatory Study (also referred to as the FIX-HF-5C Study) was designed to prospectively confirm the prespecified subgroup findings from the FIX-HF-5 Study that CCM appeared more effective in patients with EF≥25% as evidence by significant improvements in pVO_2. The FIX-HF-5C study enrolled 160 randomized subjects with a NYHA III or IV despite optimal medical treatment (OMT), LVEF 25-45% (inclusive, as quantified by the echo core lab) and narrow QRS. Efficacy was assessed by peak VO_2, per blinded core lab

assessment, at 24-weeks. The primary safety endpoint is Optimizer device and Optimizer procedure-related complications at 24-weeks, per the classification of an independent physician adjudication committee. The results of this study supplement and confirm results from prior studies in demonstrating that CCM is safe and improves peak VO2, 6-minute hall walk test, quality of life and heart failure symptoms. This data was provided to the FDA in PMA P180035 filed on September 5, 2018 and approved by the FDA on March 21, 2019. Note that although an improvement in peak VO2 was shown by Bayesian Analysis of this study, the FDA did not deem the improvement sufficient enough to be included in the final labeling for the device.

FIX HF-5C2 Confirmatory Study (US and Europe)

The FIX-HF-5C2 Confirmatory Study is multicenter, prospective, single-arm treatment only confirmatory study of the 2-lead configuration of the Optimizer Smart System. The study is designed to demonstrate improvement in exercise tolerance quantified by peak VO2 measured on cardiopulmonary exercise stress testing (CPX). The CPX data will be evaluated by an independent core lab. Subjects who receive the Optimizer Smart System under the FIX-HF-5C2 protocol will be compared to subjects in the control group of the FIX-HF-5C protocol with respect to peak V02 mean change at 24-weeks from baseline. Additionally, there will be a comparison made between the Optimizer per-protocol groups in both protocols to show there is no difference between the therapy provided by the two device configurations. Total CCM delivery (effective hours delivered) will be evaluated at the end of 24 weeks following the Optimizer implantation. The FIX-HF-5C2 Study completed enrollment and is now in the follow-up phase.

The current FIX-HF-5CA protocol allows for continued access to the 2-lead configuration of the Optimizer System for patients in the U.S. while the follow-up phase of the FIX-HF-5C2 Confirmatory Study and preparation of the market application to the FDA is in progress.

E. Summary of the known and potential risks and benefits 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 Smart pulse generator

The risks associated with implantation of the OPTIMIZER Smart 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 Smart 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 Smart 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, 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 Smart 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.

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 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 Smart device are appropriately trained in proper device programming.

n. Surgical revision of the OPTIMIZER Smart 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.

F. Description of and justification for the CCM dosage.

CCM signals are non-excitatory electrical signals delivered to the heart muscle in the left ventricle through commercially available implanted pacemaker leads. 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 a maximum voltage of 7.5 V, 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. The FIX-HF-5 Phase I and Phase II studies, FIX-HF-5B and FIX-HF-5C studies, and the FIX-HF-5C2 study have all utilized a CCM dose of 5 hour/day signal delivery paradigm. This has been clinically acceptable and for consistency, the present study shall

continue to use the 5 hour/day dose. All subjects shall receive five non-contiguous one-hour periods of CCM signal application per day, with a schedule of one hour ON and three hours 48 minutes OFF.

G. Statement of Compliance

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

H. Description of the population to be studied

Subjects entered into this study will be representative of the patient population with stable, systolic left ventricular dysfunction and moderate-to-severe symptomatic heart failure despite appropriate medical therapy. The population is generally characterized by NYHA Class III and IV symptoms and having a left ejection fraction measuring between 25 and 45% (inclusive).

II. STUDY OBJECTIVES

The primary objectives of this protocol include the following:

1. Allow ongoing access to treatment of patients suffering from moderate to severe heart failure at selected investigational sites until the PMA order has been issued by the FDA for the OPTIMIZER System.
2. Evaluate quality life, as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ).
3. Evaluate safety in the Continued Access study, and further into the post-approval study, by comparing the observed mortality rate to the predicted probability of mortality derived by the Seattle Heart Failure Model (SHFM) and the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC).

III. STUDY DESIGN

This is a multicenter, prospective, single-arm Continued Access study of the Optimizer Smart System with CCM therapy. All subjects will be followed until the PMA order has been issued by the FDA. The protocol is designed to collect adverse safety events, quality of life data and data needed for comparison with long term mortality prediction models.

A. Description of the study procedures and stages

The study will include baseline eligibility tests and assessments followed by implantation of the OPTIMIZER Smart device in eligible subjects. All subjects will be followed until the PMA order has been issued by the FDA. Additional follow-up may be required during the post market period for a minimum of 3 total follow-up years. Evaluation of subjects will be documented on electronic case report forms and will include the tests and procedures listed in **Table 1.**

Table 1. Schedule of Tests and Assessments

Tests and Assessments	Screening /Baseline	OPTIMZER Implant	2 Weeks ± 7 days	30-40 Days	6 Mo ± 1 mo	1 Year ± 1 mo	Every 6 months †
Informed Consent	X						
Medical History and Risk Factors	X						
Blood Testing*	X						
Follow-up Assessment			X		X		
NYHA Class	X				X		
Medications	X				X		
Physical Examination	X				X		
12-Lead EKG**	X						
24-Hour Holter Monitor**	X						
Echocardiogram**	X						
KCCQ	X				X	X	
Eligibility determination	X						
OPTIMIZER Smart System Implant		X					
Chest X-ray (prior to hospital discharge)		X					
OPTIMIZER Device Interrogation / Programming		X	X		X	X	X
Safety Reporting		X	X	X	X	X	X

* Baseline blood testing (Creatinine, Hgb, Lymphocyte %, Uric Acid, Total Cholesterol and Sodium) performed within 30 days before informed consent may be used for baseline testing.

** 24-Hour Holter Monitor, 12-Lead EKG and Echocardiogram test results obtained within 60 days before informed consent and performed in accordance with the protocol, may be used for eligibility determination.

† Visits shall continue every 6 months until the PMA Supplement order has been issued by the FDA.

B. Anticipated Number of Sites and Subject Recruitment Rate

Up to 350 eligible subjects may be enrolled (providing consent and implanted). Eligible study participants may be enrolled from a maximum of 40 study sites in the United States.

C. Expected duration of subject participation

All eligible subjects will be asked to participate in the study until the PMA order has been issued by the FDA. Subjects can expect to participate for up to 2 years. The sequence and duration of specific study periods are described in **Table 1**.

D. Description of the Study "stopping rules" or "discontinuation criteria"

There shall be no stopping rules or discontinuation criteria. Enrollment into the Continued Access study shall end upon the issue of the PMA order by the FDA.

E. Accountability procedures for investigational products.

Clinical investigators will be trained in the importance of investigational products accountability. Impulse Dynamics will deliver OPTIMIZER Smart System related hardware to each enrolling clinical site, including the OPTIMIZER Smart IPGs, Chargers and an OMNI Smart Programmer. IPGs are generally not stored with the site inventory but rather carried in for each implant case by the engineer.

In accordance with 21 CFR 812.140, the clinical investigator is responsible for maintaining records of receipt, use or disposition of the investigational devices including:

- the type and quantity of the device, dates of receipt, and batch numbers or code marks
- names of all persons who received, used, or disposed of each device
- the number of units of the device returned to the sponsor, repaired, or otherwise disposed of, and the reason(s) therefore.

The IDE Device Accountability Log shall be maintained and updated throughout the study.

In accordance with 21§812.110, upon completion or termination of the clinical study or the investigator's part of the study or at Impulse Dynamic's request, the investigator shall return any remaining investigational product.

F. Data to be recorded directly onto CRFs and considered to be source data.

A source document should be available for all data entered into the electronic case report forms (eCRF). A listing of the case report forms is located in Appendix C.

IV. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

A. Subject inclusion criteria

Individuals must meet all of the following inclusion criteria to be eligible to participate in the study.

1. Male and nonpregnant females who are 18 years of age or older.
2. Subjects who have a baseline ejection fraction greater than or equal to 25% and less than or equal to 45% by echocardiography.

   NOTE: Echocardiograms performed within 60 days before patient informed consent may be used to determine study eligibility with confirmed baseline medication stability.
3. Subjects who, in the opinion of the Investigator (based on the current guidelines for clinical practice), have been treated for heart failure for at least 90 days and are currently receiving appropriate, stable medical therapy during the 30 days prior to enrollment for treatment of heart failure.

   NOTE: 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).
4. Subjects who are in New York Heart Association functional Class III and IV at the time of enrollment.
5. Subjects who are willing and able to return for all follow-up visits.

B. Subject exclusion criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. 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 may not be evaluated for the protocol until a minimum of 90 days after the procedure.
2. Subjects receiving any form of inotropic support within 30 days before enrollment, including subjects on continuous IV inotrope therapy.

3. Subjects hospitalized for decompensated heart failure requiring acute treatment with intravenous loop diuretics, IV inotropes or hemofiltration within 30 days before enrollment and baseline testing.
4. Subjects who have a clinically significant amount of ambient ectopy, defined as more than 8,900 PVCs per 24 hours on baseline Holter monitoring.

   NOTE: 24-Hour Holter monitoring performed within 60 days before patient informed consent may be used to determine study eligibility. Holter readings < 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 < 8,900 per 24 hours.
5. 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.
6. Subjects who have a biventricular pacing system, an accepted indication for such a device, or QRS width of 130ms or greater.

   NOTE: Subjects with a deactivated CRT for ≥3 months may be considered for enrollment if a QRS duration is <130ms. An ECG performed within 60 days before enrollment may be used to determine study eligibility.
7. Subjects who have had a myocardial infarction within 90 days of enrollment.
8. Subjects who have mechanical tricuspid valve.
9. Subjects who have a Left Ventricular Assist Device or prior heart transplant.
10. Subjects on dialysis.
11. Subjects who are participating in another experimental protocol.

    NOTE: Control subjects enrolled in the FIX-HF-5C study may be enrolled in the current protocol after completing the 24-month vital status assessment.
12. Subjects who are unable to provide informed consent.

C. Subject withdrawal criteria and procedures specifying

A patient is considered enrolled in the study after signing the IRB-approved Informed Consent Form. All subjects who sign Informed Consent will be accounted for in the final report of this study. Subjects are free to withdraw from participation in the study at any time upon request. An investigator may terminate the subject's participation in the study if:

1. Subject does not meet one or more of the protocol selection criteria or are unable to complete one or more of the baseline assessments.
2. Non-cardiac intercurrent illness or circumstance that prohibits the subject from complying with follow-up evaluations.
3. Continued participation in the study would not be in the best interest of the subject. Subjects who become pregnant during the study shall have CCM therapy suspended.

Good faith efforts will be made to contact all subjects who have received the Optimizer System to ascertain their vital status.

Subjects with an Optimizer device who wish to withdraw from the study will have their device 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. Device removal is also an option to the subject at this time.

V. STUDY PROCEDURES AND EVALUATIONS

A. Screening Assessments

Potentially eligible subjects will be informed of the relative risks and potential benefits of participating in the study and then asked to review and sign an IRB-approved informed consent document in accordance with 21§50. A copy of the Informed Consent document template is located in Appendix B. It is recognized that each participating institution shall have their own requirements related to the wording of the informed consent document as well as HIPAA privacy laws. For each subject, a medical history, physical examination, demographic information, medication history (≥ 90 days history) and current usage of medications will be obtained.

B. Baseline Testing

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 explained in section IV.A.

Subjects will be asked to complete a Kansas City Cardiomyopathy Questionnaire (KCCQ), undergo an NYHA assessment, ECG, 24-Hour Holter,,echocardiogram, and blood testing for Creatinine, Hgb, Lymphocyte %, Uric Acid, Total Cholesterol and Sodium.

- An ECG performed within 60 days prior to enrollment may be used as the baseline test and protocol eligibility determination.
- An echocardiogram performed within 60 days prior to enrollment can be used if the baseline heart failure medications requirement was met at the time the test was performed.
- A 24-hour Holter test performed within 60 days prior to enrollment may be used as the baseline test and protocol eligibility determination. Other devices that record all heart beats over a period of 24 hours, that provide total counts of isolated ectopics, couplets, and triplets, may be used, as well (i.e., Zio patch).
- Laboratory values collected within 30 days prior to enrollment may be used for baseline testing requirements.

C. Optimizer Smart Implantation

Eligible subjects will undergo implantation of the OPTIMIZER Smart 2-lead System. Subjects will be prepared for device implantation according to procedures used at the implanting 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, cephalic or axillary vein, two ventricular leads (as specified in section II.A.4) 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 Smart IPG. To ensure that the OPTIMIZER Smart 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 Smart 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.

When the subject is stable and suitable for discharge, a separate pre-discharge chest X-ray (radiography or fluoroscopy) shall be done to rule out pneumothorax and to evaluate lead placement. CCM will be activated and observed prior to discharge with the subject on telemetry; device parameters will be adjusted as needed to ensure proper functioning. Subjects will be introduced to the battery charging system and provided a comprehensive overview on the use of this equipment. Subjects will be discharged with CCM therapy on.

D. 2-Week Follow-up Visit

Approximately 2 weeks after the OPTIMIZER Smart System implant, the subject will return for follow up. The OPTIMIZER Smart IPG will be interrogated to confirm proper functioning and parameters shall be adjusted as needed. In addition, the subject's compliance and understanding with battery charging to maintain CCM therapy ON and the cumulative CCM delivery percentage will be assessed.

E. 30-day Safety Assessment

Each subject will be called approximately 30 days after the index Optimizer Smart System implant procedure to inquire about any and all adverse events, ER visits and Hospitalizations that may have occurred. The hospital/clinic/medical record will be searched for completeness of reporting, as well.

F. 6-Month Follow-up Visit

All subjects will return for follow-up 6 months following the Optimizer Smart System implant. The visit includes a medication review, a physical examination, an NYHA classification, a KCCQ and an OPTIMIZER interrogation. The OPTIMIZER interrogation will include an assessment of the subject's compliance with battery charging to maintain CCM therapy ON and the cumulative CCM delivery percentage will be assessed. OPTIMIZER device-related adverse events (ADEs) and OPTIMIZER serious device-related adverse events (SADEs) shall be reported for the duration of the 6-month study

G. Long-term Follow-up

Following the 6 month follow-up visit, all subjects will be seen at approximately 6 month intervals at the investigational site until FDA has made a determination of device safety and efficacy. These follow-up visits shall include an OPTIMIZER device interrogation and reporting of any ADEs, SADEs, and deaths. In addition, a KCCQ is required at the 1-year visit only.

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

I. Medications/treatments permitted 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.

J. Procedures for monitoring subject compliance

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

VI. SAFETY DATA REPORTING REQUIREMENTS AND DEFINITIONS

A. Procedures for recording and reporting adverse events and Intercurrent illnesses

The following safety data and assessments will be collected for safety during the study:

1. Adverse Events (AEs) and Adverse Device Events (ADEs)

All AEs occurring within 30 days of implant will be reported, regardless of their attribution to the device or procedure. An AE 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 AE includes device failures that adversely affect the subject and/or require an intervention to correct the failure (ADE). AEs will be further classified by the Investigator for the following:

Optimizer procedure-related: The Investigator will decide whether the AE is considered to be not related, possibility related, definitely related to the Optimizer procedure.

Optimizer device-related: The Investigator will decide whether there is a logical connection between the use of the device and the occurrence of the event (meaning the relationship to the device cannot reasonably be ruled out) and classified as not related, possibility related, definitely related to the Optimizer device.

2. Serious Adverse Device Events/Effects (SADEs)

Serious Adverse Device Events/Effects (SADEs): All SADEs will be reported for as long as the subject is active in the study. An Optimizer device- or Optimizer procedure-related AE shall be classified as "serious" if there is an 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.

- The term "disability" in the definition above refers to substantial disruption of the subject's ability to conduct normal life functions.
- The term "life-threatening" in the definition above refers to an event that places the patient, in the view of the investigator, at immediate risk of death from the event as it occurred; it does not refer to an event that hypothetically might have caused death if it were more severe or left untreated.

Impulse Dynamics will review serious adverse device events and deaths to determine whether an unanticipated adverse device effect may have occurred.

3. Unanticipated Adverse Device Effect (UADE)

In accordance with CFR 21 § 812.3(s), a UADE is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

4. Mortality

All deaths, regardless of whether it is related to the study device, study procedure, or not, shall be reported.

B. Procedures for reporting UADEs

1. Investigator Reporting Obligations

   The Investigator shall report all safety events defined in section VI.A of the current protocol to Impulse Dynamics and to the reviewing IRB (as/if required according to IRB policy). Serious adverse device events (SADEs) must be reported to Impulse Dynamics within 1 business day after the Investigator learns of the event.

   According to 812.150(a), the Investigator is required to submit a report of any UADE occurring during the study to Impulse Dynamics and to the reviewing IRB as soon as possible, but in no event later than 10 working days after he/she first learns of the effect.

2. Sponsor Reporting Obligations

   In accordance with CFR 21 § 812.46, Impulse Dynamics will immediately conduct an evaluation of any UADE. If Impulse Dynamics determines that a UADE presents an unreasonable risk to subjects, it will terminate all investigations or parts of the investigations presenting that risk as soon as possible. Termination will occur no later than 5 working days after Impulse Dynamics makes this determination and no later than 15 working days after Impulse Dynamics first received notice of the effect.

VII. ASSESSMENT OF EFFECTIVENESS

Change in quality of life, as assessed by the Kansas City Cardiomyopathy Questionnaire.

VIII. ASSESSMENT OF SAFETY

Safety will be assessed by comparing the prevalence of mortality observed in the Continued Access Study (CAS) to the predicted probability of mortality derived from two validated heart failure models [MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) and SHFM (Seattle Heart Failure Model)]. The objective is to show that the observed prevalence of mortality is not worse than the derived predicted probability of mortality. Two pairwise comparisons (CAS vs. MAGGIC, CAS vs. SHFM) will be performed at 1 year and 3 years. Observed statistical differences will be noted if the two-sided p-value is less than 0.05.

A. Seattle Heart Failure Model (SHFM)

Specific baseline data will be collected in order to predict survival based on the SHFM. Computation of the SHFM score is done with 14 continuous variables and 10 categorical values; a web-based calculator is available to perform the calculation (http://www.SeattleHeartFailureModel.org).

B. Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC)

Specific baseline data will be collected in order to predict survival based on the MAGGIC Prognostic Heart Failure Survival Model. The model identifies 13 independent predictors that should be routinely available although provisions have been made by the website (www.heartfailurerisk.org) for one or two variables to be unknown for an individual.

C. Censored and Missing Data

In the SHFM and MAGGIC analyses above, subjects receiving an LVAD or heart transplant, cases of a device explants, and cases of a decision to permanently stop the therapy will be censored at the time of that change of therapy. These will be documented in the CRF, and will not be counted as an event. In any case of interim analysis, for the purpose of the Kaplan-Meier analysis, unless known otherwise, all cases that are under ongoing routine follow-up that have not yet completed the 3 years period shall be assumed to be alive and treated until the date of analysis.

Missing values may be overcome using imputation by the mean value of the cohort, or default values of the model for similar cohorts.

IX. OTHER ASSESSMENTS

Change in heart failure symptoms will be assessed using the NYHA classification assigned by a site clinician according to their standard clinical practice.

X. DIRECT ACCESS TO SOURCE/DATA DOCUMENTS

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

XI. QUALITY CONTROL AND QUALITY ASSURANCE

Quality control and quality assurance is the responsibility of the Investigator and designated 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; 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 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 protocol will include rationale for the amendment and will be approved by IRBs. Major deviations from the protocol will be recorded and included in the final study report.

XIII. DATA HANDLING AND RECORD KEEPING

The Database Management System used for this study is Clindex. Clindex was developed by Fortress Medical Systems, LLC, has been validated, and is in compliance with the FDA's regulations on electronic signatures and electronic records (21 CFR Part 11). The database resides in a SOC3 certified facility with numerous security controls in place. Data is stored in

encrypted databases that are backed up hourly and the back-ups transferred to an offsite location. Back-up files are also encrypted.

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.

APPENDIX A

CCM References

Impulse Dynamics - Articles

1. A New Algorithm for Detection and Verification of Ventricular Arrhythmia from the Left Ventricular Pressure Waveform. **Authors**: T Harel, I Shemer, S Policker, Y Mika, S Ben Haim, N Darvish. Impulse Dynamics, Tirat Carmel, Israel. Computers in Cardiology 2000; 27: p.351-354.
2. *Electric Currents Applied During the Refractory Period can Modulate Cardiac Contractility In Vitro and In Vivo*. **Authors**: Daniel Burkhoff, Itzik Shemer, Bella Felsen, Juichiro Shimizu, Yuval Mika, Marc Dickstein, David Prutchi, Nissim Darvish, Shlomo A. Ben Haim. *Heart Failure Reviews; Vol. 6, No' 1; (January 2001) p.27-34.*
3. Global Improvement in Left Ventricular Performance Observed with Cardiac Contractility Modulation is the Result of Changes in Regional Contractility. **Authors**: David J. Callans, Shmuel Fuchs, Yuval Mika, Itzhak Shemer, Ricardo Aviv, Walid Haddad, Nissim Darvish, Shlomo Ben Haim, Ran Kornowski. Heart Failure Reviews; Vol. 6, No' 1; (January 2001) p.35-44.
4. *Cardiac Contractility Modulation with the Impulse Dynamics Signal: Studies in Dogs with Chronic Heart Failure*. **Authors**: Hani N. Sabbah, Walid Haddad, Yuval Mika, Itzhak Shemer, Ricardo Aviv, Victor G. Sharov, Victor Maltseu, Bella Felzen, Albertas I. Undrovinas, Sidney Goldstein, Nissim Darvish, Shlomo A. Ben Haim. *Heart Failure Reviews; Vol. 6, No' 1; (January 2001) p. 45-53.*
5. *Electrical Modulation of Cardiac Contractility: Clinical Aspects in Congestive Heart Failure*. **Authors**: Carlo Pappone, Gabriele Vicedomini, Adriano Salvati, Carlo Meloni, Walid Haddad, Ricardo Aviv, Yuval Mika, Nissim Darvish, Yoav Kimchy, Itzhak Shemer, Yehuda Snir, David Prutchi, Shlomo A. Ben Haim, Itzhak Kronzon. *Heart Failure Reviews; Vol. 6, No' 1; (January 2001) p. 55-60.*
6. *Cardiac Contractility modulation by electric currents applied during the refractory period*. **Authors**: Satoshi Mohr, Kun-Lun He, Marc Dickstein, Yuval Mika, Juichiro Shimizu, Itzhak

Shemer, Geng-Hua Yi, Jie Wang, Shlomo Ben-Haim, and Daniel Burkhoff. *AJP Heart Circ Physiol Vol. 282, May 2002, pp 1642-47 (First published January 17, 2002).*

7. *Nonexitatory Stimulus Delivery Improves Left Ventricular Function in Hearts with Left Bundle Branch Block*. **Authors**: Nassir F. Marrouche, M.D., Stephen V. Pavia, M.D., Shaowei Zhuang, M.D., Yung-Jin Kim, M.D., Tomotsugu Tabata, M.D.,Don Wallick, Ph.D., Eduardo Saad, M.D., Ahmad Abdul-Karim, M.D., Robert Schweikert, M.D., Walid Saliba, M.D., Patrick Tchu, M.D., and Andrea Natale, M.D. The Section of Pacing and Electrophysiology, Department of Cardiovascular Medicine, The Cleveland Clinic Foundation, Cleveland, Ohio. *Journal of Cardiovascular Electrophysiology Vol 13 Issue 7 July 2002, pp 691-5.*
8. Nonexcitatory Stimulation: 2002: A Pace Odyssey **Author:** Kirstin Ellison, M.D. Editorial Comment, Journal of Cardiovascular Electrophysiology, Volume 13, No. 7, July 2002.
9. Electric Currents Applied during Refractory Period Enhance Contractility and Systolic Calcium in the Ferret Heart. **Authors**: Mohri S, Shimizu J, Mika Y, Shemer I, Wang J, Ben-Haim S, Burkhoff D. Am J Physiol Heart Circ Physiol. 2003 Apr;284(4): H1119-23. Epub 2002 Nov 21.
10. Cardiac Contractility Modulation by Electric Currents Applied During the Refractory Period in Patients with Heart Failure Secondary to Ischemic or Idiopathic Dilated Cardiomyopathy. **Authors**: Carlo Pappone, MD, PhD, Salvatore Rosanio, MD, PhD, Daniel Burkhoff, MD, PhD, Yuval Mika, DSc, Gabriele Vicedomini, MD, Giuseppe Augello, MS, Itzhak Shemer, MD, David Prutchi, DSc, Walid Haddad, PhD, Ricardo Aviv, DSc, Yehuda Snir, DSc, Itzhak Kronzon, MD, Ottavio Alfieri, MD, and Shlomo A. Ben-Haim, MD, PhD. From the Department of Cardiology, San Raffaele University Hospital, Milan, Italy, Division of Circulatory Physiology, Columbia University, New York, NY. Department of Physiology and Biophysics, Technion-Israel Institute of Technology, Haifa, Israel, and Division of Cardiology, New York University Medical Center, New York, NY. The American Journal of Cardiology, 15 December 2002, Vol. 90, Issue 12, Pages 1307-1313.
11. Cardiac Contractility Modulation With Nonexcitatory Electric Signals Improves Left Ventricular Function in Dogs With Chronic Heart Failure. **Authors**: Morita H, Suzuki G, Haddad W, Mika Y, Tanhehco EJ, Sharov VG, Goldstein S, Ben-Haim S, Sabbah HN. Departments of Medicine, Division of Cardiovascular Medicine, Henry Ford Heart and

Vascular Institute, Henry Ford Health System, Detroit, Michigan 48202, USA J Card Fail. 2003 Feb;9(1): 69-75.

12. First Human Chronic Experience with Cardiac Contractility Modulation by Non-Excitatory Electrical Currents for Treating Systolic Heart Failure (Mid-term safety and efficacy Results from a Multicenter Study) **Authors**: Carlo Pappone, MD, PhD, FACC; Giuseppe Augello, MD; Salvatore Rosanio, MD, PhD, FACC; Gabriele Vicedomini, MD; Vincenzo Santinelli, MD; Massimo Romano, MD; Eustachio Agricola, MD; Francesco Maggi, DSc; Gerhard Buchmayr, DSc; Giovanni Moretti; Yuval Mika, DSc; Shlomo A. Ben-Haim MD, PhD; Michael Wolzt, MD; Guenter Stix, MD; and Herwig Schmidinger, MD. J Cardiovasc Electrophysiol, Vol. 15, pp. 418-427, April 2004.
13. Nonexcitatory Electrical Currents for Congestive Heart Failure: Exciting or Not? Editorial Comment **Authors:** Mevan Wijetunga and Adam Strickberger Journal of Cardiovascular Electrophysiology, Vol 15, April 2004.
14. Long-Term Effects of Non-Excitatory Cardiac Contractility Modulation Electric Signals on the Progression of Heart Failure in Dogs **Authors**: Hideaki Morita, George Suzuki, Walid Haddad, Yuval Mika, Elaine J. Tanhehco, Sidney Goldstein, Shlomo Ben-Haim, Hani N. Sabbah. The European Journal of Heart Failure 2004 Mar 1;6(2): 145-50.
15. *Chronic electrical stimulation during the absolute refractory period of the myocardium improves severe heart failure*. **Authors**: Guenter Stix, Martin Borggrefe, Christian Wolpert, Gerhard Hindricks, Hans Kottkamp, Dirk Böcker, Thomas Wichter, Yuval Mika, Shlomo Ben-Haim, Daniel Burkhoff, Michael Wolzt, Herwig Schmidinger. *European Heart Journal* 2004 Apr; 25(8):650-5.
16. Nonexcitatory stimulation as novel treatment for heart failure: cause for excitement? Editorial **Authors:** Rik Willems, Karin R. Sipido European Heart Journal (2004) 25, pp. 626-628.
17. Cardiac contractility modulation by non-excitatory electrical currents. The new frontier for electrical therapy of heart failure. **Authors**: Augello G, Santinelli V, Vicedomini G, Mazzone P, Gulletta S, Maggi F, Mika Y, Chierchia G, Pappone C. Ital Heart J. 2004 Jun;5 Suppl 6:68S-75S.
18. Nonexcitatory electrical signals for enhancing ventricular contractility: rationale and initial investigations of an experimental treatment for heart failure. **Authors**: Burkhoff D, Ben-Haim SA. Am J Physiol Heart Circ Physiol. 2005 Jun;288(6):H2550-6.

19. Electrical Signals Applied during the Absolute Refractory Period: An Investigational Treatment of Advanced Heart Failure in Patients with Normal QRS Duration. **Authors**: Thomas Lawo MD, Martin Borggrefe MD, Christian Butter MD, Gerhard Hindricks MD, Herwig Schmidinger MD, Yuval Mika PhD, Daniel Burkhoff MD PhD, Carlo Pappone MD PhD, Hani N Sabbah PhD. JACC, Vol. 46, No. 12, 2005, 2230-2236.
20. Cardiac Contractility Modulation by Non-Excitatory Currents: Studies In Isolated Cardiac Muscle. **Authors**: Corinna B Brunckhorst, MD; Itzak shemer, MD; Yuval Mika, DSc; Shlomo A Ben-Haim, MD, PhD; Daniel Burkhoff, MD, PhD. European Journal of Heart Failure 8 (2006) 7-15.
21. *Treating Heart failure with Cardiac Contractility Modulation Electrical Signals.* **Authors**: Hani N. Sabbah, PhD, Ramesh C. Gupta, PhD, Sharad Rastogi, MD, Sudish Mishra, PhD, Yuval Mika, PhD, and Daniel Burkhoff, MD. *Current Heart Failure Reports* 2006, 3:21-24.
22. Non-Excitatory, Cardiac Contractility Modulation (CCM) Electrical Impulses: Feasibility Study for advanced Heart Failure in Patients with Normal QRS Duration **Authors**: Suresh B. Neelagaru, Javier E. Sanchez, Stanley K. Lau, Steven M. Greenberg, Nirav Y. Raval, Seth Worley, Jill Kalman, Andrew D. Merliss, Steven Krueger, Mark Wood, Marc Wish, Daniel Burkhoff, Koonlawee Nademanee. Heart Rhythm 3(10), October 2006, 1140-1147.
23. Enhanced Inotropic State of the Failing Left Ventricle by Cardiac Contractility Modulation Electrical Signals is Not Associated with Increased Myocardial Oxygen Consumption. **Authors**: Christian Butter MD, Ernst Wellnhofer MD, Michael Schlegl MD, Georgia Winbeck MD, Eckart Fleck MD and Hani N. Sabbah, Ph.D. Journal of Cardiac Failure. Vol. 13, No. 2, 2007, p 137.
24. Therapy with Cardiac Contractility Modulation Electrical Signals Improves Left Ventricular Function and Remodeling in Dogs with Chronic Heart Failure. **Authors**: Makoto Imai, M.D., Sharad Rastogi, M.D., Ramesh C. Gupta, Ph.D. Sudhish Mishra, Ph.D., Victor G. Sharov, M.D., Ph.D., Yuval Mika, Ph.D., Benny Rousso, Ph.D., Daniel Burkhoff, M.D., Ph.D., FACC, Shlomo Ben-Haim, M.D., Ph.D., Hani N. Sabbah, Ph.D., FACC. Journal of the American College of Cardiology. Vol.49, No.21, May 29, 2007, 2120-8.
25. First use of cardiac contractility modulation (CCM) in a patient failing CRT therapy: Clinical and technical aspects of combined therapies. **Authors**: Christian Butter, Jurgen Meyhofer,

Martin Seifert, Michael Neuss, Hans-Heinrich Minden. European Journal of Heart Failure, 2007, Volume 9, Issue 9, Pages 955-958.

26. Effects of Chronic Therapy with Cardiac Contractility Modulation Electrical Signals on Cytoskeletal Proteins and Matrix Metalloproteinases in Dogs with Heart Failure. **Authors:** Sharad Rastogi, Sudish Mishra, Valerio Zacà, Yuval Mika, Benny Rousso, Hani N. Sabbah. CARDIOLOGY. 2007 Dec 12;110(4):230-237.

27. Anaesthesia and cardiac contractility modulation **Authors**: Huschak G, Schmidt-Runke H, Ruffert H. Eur J Anaesthesiol 2007; 24:819-25.

28. Randomized, Double Blind Study of Non-Excitatory, Cardiac Contractility Modulation (CCM) Electrical Impulses for Symptomatic Heart Failure **Authors:** Martin M. Borggrefe, Thomas Lawo, Christian Butter, Herwig Schmidinger, Maurizio Lunati, Burkert Pieske, A. Ramdat Misier, Antonio Curnis, Dirk Böcker, Andrew Remppis, Joseph Kautzner, Markus Stühlinger, Christophe Leclerq, Miloš Táborský, Maria Frigerio, Michael Parides, Daniel Burkhoff, and Gerhard Hindricks. European Heart Journal. 2008 Apr;*29*(*8*):*1019-28.*

29. Cardiac Contractility Modulation Electrical Signals Improve Myocardial Gene Expression in Patients with Heart Failure **Authors:** Christian Butter, Sharad Rastogi, Hans-Heinrich Minden, Jürgen Meyhöfer, Daniel Burkhoff and Hani N. Sabbah. J Am Coll Cardiol. 2008 May 6;*51*(*18*):*1784-9*.

30. A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation in patients with systolic heart failure: Rationale, design, and baseline patient characteristics. **Authors:** William T. Abraham, Daniel Burkhoff, Koonlawee Nademanee, Peter Carson, Robert Bourge, Kenneth A. Ellenbogen, Michael Parides, and Alan Kadish, On behalf of the FIX-HF-5 Investigators and Coordinator. Am Heart J. 2008 Oct; *156*(*4*):*641-648.*

31. Cardiac contractility modulation in non-responders to cardiac resynchronization therapy. **Authors:** Nägele H*, Behrens S, Eisermann C. Europace. 2008; Dec;10(12):1375-80. Epub 2008 Sep 5.

32. Improving left ventricular contractility by stimulation during the absolute refractory period—cardiac contractility modulation (CCM). **Authors:** Seifert M, Hoffmann J, Meyhöfer J, Butter C. Herzschrittmacherther Elektrophysiol. 2008 Dec;19 Suppl 1:69-76. German.

33. "Responder Analysis" for Assessing Effectiveness of Heart Failure Therapies based on Measures of Exercise Tolerance. **Authors:** Daniel Burkhoff MD PhD, Michael Parides PhD,

Martin Borggrefe MD, William T Abraham MD and Alan Kadish MD. Journal of Cardiac Failure 2009 Mar;15(2):108-15. Epub 2008 Dec12.

34. Cardiac contractility modulation electrical signals normalize activity, expression, and phosphorylation of the Na+-Ca2+ exchanger in heart failure. **Authors:** Gupta RC, Mishra S, Wang M, Jiang A, Rastogi S, Rousso B, Mika Y, Sabbah HN. J Card Fail. 2009 Feb;15(1): 48-56. Epub 2008 Oct 15.
35. Cardiac contractility modulation: a new option for treating systolic heart failure. **Authors:** Rottlaender D, Michels G, Hoppe UC. Dtsch Med Wochenschr. 2009 Mar;134(13):639-43. Epub 2009 Mar 17. Review. German.
36. Biventricular and novel pacing mechanisms in heart failure. **Authors:** Salazar C, Abraham WT. Curr Heart Fail Rep. 2009 Mar;6(1):14-8.
37. *High sensing integrity counter in a patient with a Sprint Fidelis defibrillation lead: What is the cause?* **Authors:** Bich Lien Nguyen, MD, Charles Swedlow, MD, FHRS, Carlo Gaudio, MD, Eli S. Gang, MD. Heart Rhythm, Vol 6, No 4, April 2009.
38. *Impact of Cardiac Contractility Modulation on Left Ventricular Global and Regional Function and Remodeling.* **Authors:** Cheuk-Man Yu, MD, FRCP, FRACP; Joseph Yat-Sun Chan, FHKAM; Qing Zhang, MM, PhD; Gabriel WK Yip, MD, FACC; Yat-Yin Lam, MRCP; Anna Chan, FHKAM; Daniel Burkhoff, MD, PhD; Pui-Wai Lee, MRCP; Jeffrey Wing-Hong Fung, MD, FRCP. *JACC* Cardiovasc Imaging. 2009 Dec;2(12):1341-9.
39. Clinical trials update from the American College of Cardiology 2009: ADMIRE-HF, PRIMA, STICH, REVERSE, IRIS, partial ventricular support, FIX-HF-5, vagal stimulation, REVIVAL-3, pre-RELAX-AHF, ACTIVE-A, HF-ACTION, JUPITER, AURORA, and OMEGA. **Authors:** Cleland JG, Coletta AP, Clark AL, Cullington D., Eur J Heart Fail 2009; 11:622-30.
40. Ca2+-Binding Proteins in Dogs with Heart Failure: Effects of Cardiac Contractility Modulation Electrical Signals **Authors**: Ramesh C. Gupta, Sudhish Mishra, Sharad Rastogi, Mengjum Wang, Benny Rousso, Yuval Mika, Andrew Remppis, Hani N. Sabbah Clinical and Translational Science, Volume 2, Issue 3, Date: June 2009, Pages: 211-215.
41. Progress in cardiac pacing] Authors: Martinez FJ, Fidalgo Andres ML, Barba PR, Sancho-Tello de Carranza MJ. Rev Esp Cardiol 2009; 62 Suppl 1:117-28.

42. Cardiac Contractility Modulation by Electrical Signals Applied during the Absolute Refractory Period as a Treatment for Chronic Heart Failure **Authors:** Daniel Burkhoff, Hani N. Sabbah, Christian Butter, Yuval Mika and Martin Borggrefe. Chapter 4 (page 44) in the book Heart Failure Device Management edited by Arthur M. Feldman. Published by Wiley-Blackwell, January 2010.
43. The ventilatory anaerobic threshold in heart failure: a multicenter evaluation of reliability **Authors**: Myers J, Goldsmith RL, Keteyian SJ, et al. J Card Fail 2010; 16:76-83.
44. Effects of Electric Stimulations Applied during Absolute Refractory Period on Cardiac Function of Rabbits with Heart Failure **Authors:** Haizhu Zhang, Changcong Cui, Dayi Hu. J. Hauzhong Univ Sci Technol. 2010; 30(2): 155-158.
45. *A Randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure* **Authors**: Alan Kadish, MD,a ,s Koonlawee Nademanee, MD,b,s Kent Volosin, MD, Steven Krueger, MD, Suresh Neelagaru, MD, Nirav Raval, MD, Owen Obel, MD, Stanislav Weiner, MD, Marc Wish, MD, Peter Carson, MD, Kenneth Ellenbogen, MD, Robert Bourge, MD, Michael Parides, PhD, Richard P. Chiacchierini, PhD, Rochelle Goldsmith, PhD, Sidney Goldstein, MD, Yuval Mika, PhD, Daniel Burkhoff, MD PhD, and William T. Abraham, MD. *American Heart Journal*, Volume 161, Number 2, February 2011, pages 329-337.e2.
46. Subgroup Analysis of a Randomized Controlled Trial Evaluating the Safety and Efficacy of Cardiac Contractility Modulation in Advanced Heart Failure. **Authors:** William T. Abraham, Koonlawee Nademanee, Kent Volosin, Steven Krueger, Suresh Neelagaru, Nirav Raval, Owen Obel, Stanislav Weiner, Marc Wish, et al. Journal of Cardiac Failure Vol. 17 No. 9 2011.
47. Does Contractility Modulation Have a Role in the Treatment of Heart Failure? **Author:** Daniel Burkhoff. Curr Heart Fail Rep. ePub 09 June 2011.
48. The effect of device-based cardiac contractility modulation therapy on myocardial efficiency and oxidative metabolism in patients with heart failure **Authors:** Georg Goliasch, Aliasghar Khorsand, Matthias Schütz, Georgios Karanikas, Cesar Khazen, Heinz Sochor, Herwig Schmidinger, Michael wolzt, Senta Graf. Eur J Nucl Med Mol Imaging DOI 10.1007/s00259-011-1977-8 (published online 15 November 2011).

49. Improvement of left ventricular contractility by stimulation during the absolute refractory period (German) Verbesserung der linksventrikulären Kontraktilität durch Stimulation in der absoluten Refraktärperiode. **Author:** Christian Butter. Herzschr Elektrophys 2011; 22: 37-33.
50. Cardiac contractility modulation as new device based therapy option for Heart failure patients (German) Neue apparative Therapie optionen bei Herzinsuffiziens Kardiale Kontraktilitätsmodulation. **Authors:** Kai Mortensen. Cardiovasc 2011; 2: 51-55.
51. Therapy of chronic heart failure by cardiac contractility modulation (CCM) (German) Therapie der chronischen Herzinsuffizienz durch kardiale Kontraktionmodulation (CCM). **Authors:** Tönnis T, Kuck KH. Herz 2011; 36: 600-607.
52. Therapy options for systolic heart failure by implementing new study results (German) Systolische Herzinsuffizienz Therapeutische Möglichketien durch Implementierung neuer Studienergebnisse. **Author:** Rolf Wachter. Klinikarzt 2011; 40(4): 192-195.
53. *Clinical effects of cardiac contractility modulation (CCM) as a treatment for chronic heart failure.* **Authors:** Martin Borggrefe, Daniel Burkhoff, Eur J Heart Fail. 2012;14(7):703-12..
54. Comparison of left ventricular reverse remodeling induced by cardiac contractility modulation and cardiac resynchronization therapy in heart failure patients with different QRS durations. **Authors:** Qing Zhang, Yat-Sun Chan, Yu-Jia Liang, Fang Fang, Yat-Yin Lam, Chin-Pang Chan, Alex Pui-Wei Lee, Karl Chi-Yuen Chan, Eugene B. Wu, Cheuk-Man Yu. International journal of cardiology 2012 (in press).
55. The Economic Benefit of Cardiac Contractility Modulation Therapy for Heart Failure Patients in the United Kingdom. A Market Research Project. **Authors**: Joao Jorge, Prof. A Noble. Trinity Term 2012.
56. Electrical therapy of heartfailure (German) Elektrische Therapie der Herzinsuffizienz. Authors: Kuschyk J, Borggrefe M. Herzinsuffizienz 2013; up2date 9: 37-53.
57. Inconsistencies in the development of the ESC Clinical Practice Guidelines for Heart Failure. **Authors:** Andrew J. Stewart Coats, Louise G. Shewan. International Journal of Cardiology 2013 (in press).
58. Cardiac contractility modulation therapy in advanced systolic heart failure. Lyon AR, Samara MA, Feldman DS. Nat Rev Cardiol. 2013;10(10):584-98.

59. New devices in heart failure: an European Heart Rhythm Association report: developed by the European Heart Rhythm Association; endorsed by the Heart Failure Association. Kuck KH, Bordachar P, Borggrefe M, et al. Europace. 2014;16(1):109-28.
60. Effects of cardiac contractility modulation by non-excitatory electrical stimulation on exercise capacity and quality of life: an individual patient's data meta-analysis of randomized controlled trials. Giallauria F, Vigorito C, Piepoli MF, Stewart coats AJ. Int J Cardiol. 2014;175(2):3527.
61. Long term impact of cardiac contractility modulation on QRS duration. Röger S, Michels J, Heggemann F, et al. J Electrocardiol. 2014;47(6):936-40.
62. Efficacy and survival in patients with cardiac contractility modulation: Long-term single center experience in 81 patients. Kuschyk J, Roeger S, Schneider R, et al. Int J Cardiol. 2015;183C:76-81.
63. A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation in patients with moderately reduced left ventricular ejection fraction and a narrow QRS duration: study rationale and design. **Authors:** Abraham WT, Lindenfeld J, Reddy VY, Hasenfuss G, Kuck KH, Boscardin J, Gibbons R, Burkhoff D; FIX-HF-5C Investigators and Coordinators. J Card Fail. 2015 Jan;21(1):16-23.
64. Improvement of long-term survival by cardiac contractility modulation in heart failure patients: A case-control study. Liu Ming, Fang Fang, Luo Xiu Xia, et al. Int J Cardiol.2016; 21826.
65. Long-term survival with Cardiac Contractility Modulation in patients with NYHA II or III symptoms and normal QRS duration. Kloppe A, Lawo T, Mijic D, et al. Int J Cardiol.2016; 219 – 295.
66. A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation. William T. Abraham, MD, Karl-Heinz Kuck, MD, Rochelle L. Goldsmith, PHD, JoAnn Lindenfeld, MD, Vivek Y. Reddy, MD, Peter E. Carson, MD, Douglas L. Mann, MD, Benjamin Saville, PHD, Helen Parise, SCD, Rodrigo Chan, MD, Phi Wiegn, MD, Jeffrey L. Hastings, MD, Andrew J. Kaplan, MD, Frank Edelmann, MD, Lars Luthje, MD, Rami Kahwash, MD, Gery F. Tomassoni, MD, David D. Gutterman, MD, Angela Stagg, BS, Daniel Burkhoff, MD, PHD, Gerd Hasenfuß, MD. JACC: Heart Failure, Volume 6, Issue 10, October 2018, Pages 874-883.

Appendix B

Informed Consent Template

Subject ID Number: ___ ___ - ___ ___ ___

FIX-HF-5CA: Continued Access Protocol for the Evaluation of the OPTIMIZER Smart System in Subjects with Moderate-to-Severe Heart Failure with Ejection Fraction between 25% and 45%

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 Smart System. The experimental treatment delivered by the Optimizer Smart System for stimulating the heart muscle with an electrical signal is called cardiac contractility modulation treatment, also referred to as CCM treatment.

Research

You are being asked to consider voluntary participation in a research study of CCM treatment with the Optimizer Smart 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

You will be expected to come in for study assessments and procedures for approximately 2 years. You will be asked to return 2 weeks after the Optimizer Smart implant procedure and 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. If FDA reviews the study and requires a patient registry, you will be asked to join the registry at that time, for additional follow-up.

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
- an assessment of your current heart failure symptoms
- an electrocardiogram (to check the electrical activity in your heart)
- a 24-hour Holter monitor test (a tape recording of your heart rhythm over the course of an entire day)
- an echocardiogram (to check the strength of your heart)
- a questionnaire that asks you about your heart failure symptoms
- blood will be taken from your arm (approximately 2 tablespoons are required for testing)

In some cases, your doctor may be able to use an echocardiogram, 24-hour Holter or electrocardiogram performed within 60 days prior to your consent to enroll in this study and blood test results reported within 30 days prior to your consent.

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 offered to you at this time.

If the results of these tests indicate that you are eligible to participate, you will be scheduled for implant of the Optimizer Smart System. Additional testing in accordance with the procedures followed by your institution, and may include additional blood testing, urinalysis, a chest x-ray and if you are a woman of childbearing potential, a pregnancy test. These procedures vary at each institution, so your doctor will discuss them with you.

The implant procedure 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 institution. 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 two electrical wires (leads) that connect the main component of the Optimizer Smart 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 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 Smart System is functioning properly. 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).

Prior to being discharged, you will have a chest X-ray and the Optimizer Smart System will be turned on. The Optimizer Smart 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 or surgical center either on the same day or the day after the implant procedure.

You will be asked to return for a follow-up visit two weeks after the Optimizer Smart System implant so the device can be checked to make sure it is working properly and will

be adjusted if necessary. You will also receive additional instructions on when and how to use the battery charger.

The study coordinator will contact you by telephone approximately 4-5 weeks after the implant procedure to ask if you have been doing since the last study visit.

You will be asked to return for a follow-up visit 6 months following the Optimizer Smart System implant. During this visit, you will undergo medication review, physical examination, Optimizer Smart device evaluation, completion of the questionnaire about symptoms you have during your daily life, and an assessment of your current heart failure symptoms.

You will be asked to return every 6 months thereafter for an Optimizer Smart device interrogation and completion of the questionnaire (at the 1-year visit only), until FDA completes their review of this study. If you suspect that you have become pregnant while participating in the study, you must contact the study doctor immediately to have the device therapy turned off.

Foreseeable Risks Associated with Study Participation

Risks Associated with the OPTIMIZER Smart System Implant and CCM Treatment

The risks associated with implanting the Optimizer Smart 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 Smart 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 Smart 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 Smart 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 Smart 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 Smart 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 Smart 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 Smart 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.

Risk from Blood Draw

Having your blood drawn is a simple procedure and complications are extremely rare. It can be difficult to take blood from people with small veins. The lab technician may be unable to locate a vein, or once the needle is inside the arm or hand, they may have to move the needle around in order to draw blood. This can cause a sharp pain or a stinging sensation. Rare complications include:

- pain or bruising at the point where the blood is taken
- infection at the needle site
- lightheadedness or fainting

Unknown Risks

Because the Optimizer Smart System is an experimental device, the application of CCM treatment to your heart may involve risks that are currently unknown. You will be notified

of any additional risks that become known during the study that may affect your decision of whether to continue in the study.

Reasonably Expected Benefits to You and to Others

Your heart failure symptoms may improve as a result of receiving CCM treatment and this may help you exercise more or feel better. The study will determine the degree to which these benefits occur. 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 https://clinicaltrials.gov/show/NCT03102437 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.

Costs

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

- The Optimizer Smart System implant hospitalization
- The Optimizer Smart System implant procedure, including anesthesia
- The Optimizer Smart System device
- Pre-discharge chest x-ray

You and your insurance provider will be responsible for paying these costs including any co-pays, co-insurance or deductibles. 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 Smart System implant hospitalization as explained earlier.

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 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.

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

APPENDIX C

Case Report Form Listing for the FIX-HF-5CA Study

Data for this study will be recorded into data entry screens using the Clindex electronic data capture (EDC) system. The following is a list of the electronic Case Report Forms:

Screening and Baseline Forms:

- Demographics
- Medical History and Risk Factors
- Physical and Assessments
- Medications
- Baseline Laboratory Values
- NYHA Classification
- Kansas City Cardiomyopathy Questionnaire
- Concomitant Cardiac Devices
- Eligibility Determination

Optimizer Index Procedure Information

- Intraoperative Event(s)
- OPTIMIZER Smart Subject Training
- Discharge

Optimizer Revision/Replacement/Removal Procedure

- Intraoperative Event(s)

Follow-up Assessment Forms:

- OPTIMIZER Interrogation
- Physical and Assessments
- Medications
- Kansas City Cardiomyopathy Questionnaire

Miscellaneous Forms

- End of Study/Withdrawal
- Protocol Deviation

Safety Event Forms

- Adverse Event Form
- Hospitalization Log
- Mortality Form

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

1. Program the ICD so that it does not deliver antitachycardia therapy during this test.
2. Program the sensing windows of the Optimizer IPG and ensure that it 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 or undersensing during normal sinus rhythm that cannot be resolved through reprogramming or lead repositioning.
4. While CCM therapy is being delivered, ensure that CCM therapy does not cause inappropriate inhibition of bradycardia pacing. In patients that require bradycardia pacing, activate CCM therapy during pacing and evaluate the real-time intracardiac electrograms and marker channels to ensure that CCM therapy does not cause inappropriate inhibition of bradycardia pacing therapy that cannot be resolved through reprogramming or lead repositioning.
5. At the implanting physician's discretion, program the ICD to detect and convert an induced ventricular tachyarrhythmia. Program the Optimizer Smart 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.