IMPULSE DYNAMICS

Hope is Here

OPTIMIZER® Smart Implantable Pulse Generator

INSTRUCTIONS FOR USE

Federal (US) law restricts this device to sale by or on the order of a physician

Part No.: 13-290-008-01-US Rev 04

Impulse Dynamics (USA), Inc
50 Lake Center Executive Parkway
Suite 100, 401 Route 73 N, Bldg. 50
Marlton, NJ 08053

U.S.A.

The information provided in this document may change without prior notice.

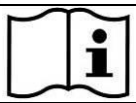
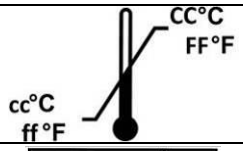
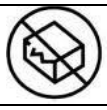
Please read the complete documentation provided before you use the device.

The OPTIMIZER® Smart system and the CCM™ technology are protected by several U.S. Patents. For an up-to-date list of relevant patents and patent applications, visit our patents page: http://www.impulse-dynamics.com/us/patents.

TABLE OF CONTENTS

THIS PAGE INTENTIONALLY LEFT BLANK

EXPLANATION OF SYMBOLS ON LABELS

SYMBOL	DESCRIPTION
	Manufacturer
	Date of Manufacture
	Consult instructions for use.
	Caution, consult accompanying documents
	Transport Temperature Limits
	Sterilized with Ethylene Oxide
	Use By
	Do Not Reuse
	Part Number
	Lot Number
	Serial Number
	Open Here
	Torque Wrench
	Port Plug
	Do Not Use if Package is Damaged

THIS PAGE INTENTIONALLY LEFT BLANK

1. THE OPTIMIZER SMART SYSTEM: AN OVERVIEW

The OPTIMIZER Smart system is intended for the treatment of moderate to severe heart failure, as defined in the Indication for Use (Section 2)." The system comprises the following components:

- Programmable OPTIMIZER Smart Implantable Pulse Generator (IPG), Model CCM X10; port plug, #2 torque wrench for securing the implanted leads
- OMNI Smart Programmer, model OMNI™ II (with OMNI Smart Software)
- OPTIMIZER Smart Charger, model Mini Charger
- Implantable leads: 2 ventricular leads.

1.1 Description of the OPTIMIZER Smart IPG

The OPTIMIZER Smart Implantable Pulse Generator (IPG) is a programmable device with an internal battery and telemetry functions. The system is intended to treat heart failure, a condition wherein the heart muscle does not pump blood as well as it should, resulting in reduced cardiac output. The OPTIMIZER Smart IPG monitors the heart's intrinsic activity and delivers CCM™ signals to cardiac tissue during the ventricular absolute refractory period, when the cardiac tissue is not capable of activation, thus rendering the CCM™ signal as non-excitatory. CCM™ signal delivery is synchronized with the detected local electrical activity and is capable of achieving the desired effect on the tissue, i.e. treating heart failure by increasing the cardiac output, or increasing the contractility of cardiac muscle.

The above-mentioned programmability of the OPTIMIZER Smart IPG implies that medical personnel can tailor the operating parameters to each patient's individual requirements with the OMNI Smart Programmer. The OPTIMIZER Smart IPG is powered by a rechargeable battery (see Section 1.4), which can be recharged transcutaneously by inductive power transfer with the OPTIMIZER Mini Charger.

The OPTIMIZER Smart IPG and the OMNI Smart Programmer communicate via telemetry (for details, see Appendix III). Telemetry is used for IPG programming as well as for obtaining diagnostic data by device interrogation. The programmer records device data, maintains a system log, stores standard programs for later use, provides an option to program "safe" parameters in an emergency, etc.

The OPTIMIZER Smart IPG is connected to two (2) leads that are implanted in the right ventricle. The OPTIMIZER Smart IPG is compatible with standard pacemaker leads equipped with IS-1 connectors.

The implanting physician can select any standard ventricular pacing leads with the following characteristics:

- Bipolar lead approved for transvenous intracardiac ventricular pacing.
- Standard IS-1 bipolar connector.
- Maximum lead diameter 8 French
- Active fixation with electrically-active corkscrew distal electrode with a minimal electrically-active surface area of 3.6 mm2.
- Distal (Tip) electrode coated with low-polarization coating (e.g. titanium nitride or iridium oxide).
- Proximal (Ring) electrode electrically-active surface of at least 3.6 mm2, and Tip-Ring spacing between 8 and 30 mm
- Maximum total wire resistance of 200 Ω

Note: The leads qualified for delivering CCM signals from OPTIMIZER IPGs must be commercial models that are FDA approved.

Pacing Leads Suitable for use with the OPTIMIZER IPG for CCM Signal Delivery Current Offerings as of January 2, 2019

Requirement for CCM	**Pacing Leads Suitable for use with OPTIMIZER IPG**					
	Medtronic CapSureFix Novus MRI™ SureScan™ 4076, 5076, 5086 Leads	**Medtronic SelectSecure™ MRI SureScan™ 3830 Lead**	**Abbott (St Jude) 2088TC Tendril STS lead**	**Abbott (St Jude) LPA1200M Tendril MRI Lead**	**Boston Scientific Ingevity 7740, 7741, 7742 and Ingevity+ 7840, 7841, 7842 Leads**	**Biotronik Solia-S Leads**
Bipolar lead approved for transvenous intracardiac ventricular pacing	YES	YES	YES	YES	YES	YES
Standard IS-1 bipolar connector	YES	YES	YES	YES	YES	YES
Active fixation with electrically-active corkscrew distal electrode	YES, 4.2 mm^2	YES, 3.6 mm^2	YES, 6.9 mm^2	YES, 6.0 mm^2	YES, 4.5 mm^2	YES, 4.5 mm^2

Requirement for CCM	Pacing Leads Suitable for use with OPTIMIZER IPG					
	Medtronic CapSureFix Novus MRI™ SureScan™ 4076, 5076, 5086 Leads	**Medtronic SelectSecure™ MRI SureScan™ 3830 Lead**	**Abbott (St Jude) 2088TC Tendril STS lead**	**Abbott (St Jude) LPA1200M Tendril MRI Lead**	**Boston Scientific Ingevity 7740, 7741, 7742 and Ingevity+ 7840, 7841, 7842 Leads**	**Biotronik Solia-S Leads**
with a minimal electrically-active surface area of 3.6 mm^2						
Distal electrode coated with low-polarization coating (e.g. titanium nitride or iridium oxide)	YES, titanium nitride coating	YES, titanium nitride coating	YES, titanium nitride coating	YES, titanium nitride coating	YES, IROX™ (iridium oxide) coating	YES, "Fractal Iridium" (iridium oxide) coating

1.2 OPTIMIZER Smart IPG Lead Connectors

The connector block accepts three (3) bipolar IS-1-BI connectors. The terminals are marked as follows:

- "A": Atrium In 2-Lead mode operation, the "A" port is plugged with a silicone plug provided with the IPG.
- "V": Ventricle
- "LS": Local sense

1.3 OPTIMIZER Smart IPG Physical Characteristics

Height (mm)	69.4 ± 2.0
Width (mm)	47.5 ± 0.5
Thickness (mm)	11.5 ± 0.5
Volume (cm^3)	30.5 ± 0.5
Mass (g)	46 ± 3.0
Exposed metallic surface[a] (cm^2)	58.1
X-ray ID The ID comprises the following 3 elements: • Impulse Dynamics Manufacturer ID: "ID" • Model number code: "OS" for OPTIMIZER Smart	**ID OS y** "y" is replaced by the letter code for the year of manufacture (see Appendix I).

• Year code: A for 2015, B for 2016, C for 2017, etc.	
Materials in contact with human tissue[b]	Titanium, Epoxy resin, Silicone rubber
Lead connectors	3.2 mm; IS-1/VS-1

[a] When using unipolar ventricular or atrial sensing, the case of the OPTIMIZER Smart device serves as indifferent electrode. The local sense (LS) polarity is always bipolar.

[b] Tests have revealed that these materials are biocompatible. The OPTIMIZER Smart IPG does not cause any temperature elevation capable of damaging the surrounding tissue.

Figure 1: OPTIMIZER Smart IPG (front view)

Figure 2: OPTIMIZER Smart IPG (back view)

1.4 OPTIMIZER Smart IPG Battery

The OPTIMIZER Smart IPG is powered by a Model QL0200I-A lithium-ion battery (Li-Ion) manufactured by Quallion and has a usable capacity of 0.2 Ah. The current consumption of the OPTIMIZER Smart IPG is highly dependent on the energy of the CCM™ signals delivered to the patient.

1.5 OPTIMIZER Smart IPG Rechargeable Battery Behavior

The battery voltage of the OPTIMIZER Smart IPG, when its rechargeable battery is fully charged, is approximately 4.1 V. When battery voltage falls to 3.3 V, the device places itself in Standby (OOO) mode and stops performing any function except telemetric communication with the Programmer and OPTIMIZER Mini Charger. The device will return to normal behavior once the voltage rises above 3.4 V. If the battery voltage drops below 3.0 V, the device disconnects its circuitry from the battery and stops performing any function, including telemetric communication with the Programmer. The device will return to Standby (OOO) mode when the apparent battery voltage exceeds 3.0V. The latter can be achieved by initiating a recharging session since the induced voltage in the IPG's charging circuit exceeds 3.0 V and the IPG can be directly powered from the inductively transferred energy.

It is therefore recommended to charge the OPTIMIZER Mini Charger at least every week. Recharging is also recommended if the device is interrogated and the battery level is at or below 3.5V.

1.6 User Profile and Training

The operators of the OPTIMIZER Smart System include patients, physicians (and trained medical personnel who assist them) and Impulse Dynamics Representatives. Physicians, medical personnel and Company representatives shall be familiar with operation of electronic medical equipment, particularly IPGs, and programmers.

Physicians and medical personnel will have participated in a Company-sponsored training program which will provide both theoretical and hands on training regarding the technology, device features and detailed operating instruction for the IPG, the programmer, and patient charger. The need for future retraining regarding the OPTIMIZER Smart System is determined by Company personnel based on the user's individual implant history and frequency.

Patient training will be limited to the use of the OPTIMIZER Mini Charger and will be provided by Impulse Dynamics Representatives post implant.

2. INDICATIONS[1]

The OPTIMIZER Smart System, which delivers CCM™ therapy, is indicated to improve 6 minute hall walk, quality of life, and functional status of NYHA Class III heart failure patients who remain symptomatic despite guideline directed medical therapy, who are in normal sinus rhythm, are not indicated for CRT, and have a left ventricular ejection fraction ranging from 25% to 45%.

The OPTIMIZER Smart system delivers non-excitatory CCM™ signals to the heart and has no pacemaker or ICD functions.

3. CONTRAINDICATIONS AND PRECAUTIONS

Use of the OPTIMIZER Smart system is **contraindicated** in:

1. Patients with a mechanical tricuspid valve
2. Patients in whom vascular access for implantation of the leads cannot be obtained

4. WARNINGS

4.1 Potential Complications of Device Implantation

Just like any surgical procedure, implantation of an OPTIMIZER Smart IPG is associated with a certain risk. Complications of IPG implantation reported in the literature include, but are not limited to: arrhythmias induced by the IPG, including life-threatening arrhythmias (e.g. ventricular fibrillation), infection, skin necrosis, device migration,

[1] The safety and performance of the OPTIMIZER Smart System is based on clinical investigations conducted with the prior generation device, the OPTIMIZER IVs and III Systems given the similarities between the Systems with regard to function, intended use, design characteristics, and the CCM™ signals. Summaries of these studies are available on Impulse Dynamics' website.

(http://www.impulse-dynamics.com/int/for-physicians/clinical-data/)

hematoma formation, seroma and histotoxic reactions (also see: Potential Adverse Effects, Section 6).

Programming high sensitivities (i.e. sensitivity settings less than 2 mV) may increase the system's susceptibility to electromagnetic interference, which could either inhibit or trigger signal delivery.

Acute and chronic complications reported in the literature include, but are not limited to: lead fracture, lead displacement, ventricular perforation, and rare cases of pericardial tamponade. Perforation of the ventricular wall can induce direct stimulation of the phrenic nerve or the diaphragm. An impedance change demonstrated on a check-up can be indicative of lead fracture, lead displacement, or perforation (also see: Potential Adverse Effects, Section 6).

In very rare cases (<1%), transvenous lead placement can also lead to venous thrombosis and subsequent SVC syndrome.

Loss of sensing shortly after implant can be the result of lead displacement. In addition, loss of CCM™ signal delivery could be due to a lead fracture.

4.1.1 Atrial and Ventricular Arrhythmias Potentially Caused by Lead Implantation

As noted above, the use of transvenous leads may lead to arrhythmias, some of which may be life-threatening such as ventricular fibrillation and ventricular tachycardia. The use of screw-in leads such as those used for CCM™ signal delivery also have the potential of causing conduction disturbances such as bundle branch block. These can be minimized by performing the implant with the use of fluoroscopic guidance, ensuring that the leads are in appropriate position prior to fixation and by limiting the number of lead manipulations. Please read and follow all directions of the original Physician Manual for the leads that you intend to use to minimize adverse events connected to lead implantation.

4.1.2 Ventricular Arrhythmias Potentially Caused by CCM™ Signals

CCM™ signals are of greater strength than that of typical pacing pulses and are thus capable of eliciting activation of cardiac tissue when delivered outside of the absolute refractory period. CCM™ signals delivered outside of the ventricular absolute refractory period thus have the potential of causing signal-induced arrhythmias (some of which may be life-threatening, such as ventricular fibrillation and tachycardia). For this reason, it is imperative that CCM™ signal delivery parameters be chosen carefully. Most importantly, the various settings related to conditions that inhibit CCM™ signal delivery (e.g. Long AV Delay, Short AV Delay, LS Alert Window, refractory periods, and IEGM sensitivities) must be selected to allow delivery of CCM™ signals only on normally conducted (e.g. non-arrhythmic) beats, but inhibit them on beats of suspected ectopic or premature origin.

In addition, CCM™ signals may cause changes in the electrical conduction of tissue. For this reason, the delivery of CCM™ signals to the ventricular septum has the potential of causing bundle branch block that could lead to bradycardia. Through similar mechanisms, CCM™-induced changes in the electrical

conduction of the myocardium have the potential of inducing tissue refractoriness that may facilitate the induction of reentrant tachyrrhythmias. It is recommended that the patient's rhythm be monitored carefully for changes in rhythm when CCM™ signals are delivered during lead implantation, as well as during first activation of the OPTIMIZER Smart IPG and subsequent follow-up visits. Changes in ventricular rhythm caused by the delivery of CCM™ signals may require relocating the leads, as well as reprogramming the CCM™ delay and amplitude to settings that do not cause changes in the patient's ventricular rhythm.

4.1.3 Atrial Arrhythmias Potentially Caused by CCM™ Signals

Atrial and supraventricular arrhythmias could theoretically be initiated when CCM™-induced ventricular activity is conducted retrograde to the atria, resulting in premature atrial depolarization. The OPTIMIZER Smart IPG may sense the ventricular activation resulting from the retrograde-induced atrial event and deliver CCM™ as programmed. In addition, strong CCM™ signals delivered through leads implanted in basal position close to the atria have the potential of directly stimulating the atria. If CCM™ delivery causes atrial activation through either of these mechanisms, and the atrial signal is then conducted to the ventricles, the cycle may develop into a condition similar to pacemaker-mediated tachycardia (PMT).

The main variables that may have an impact on CCM™ events leading to atrial activation are the location of lead placement on the right ventricular septum, CCM™ amplitude, and CCM™ delay. To prevent the occurrence of atrial arrhythmias due to CCM™ signal delivery, it is recommended that basal lead implant locations be avoided. The potential for direct atrial activation by CCM™ signals can be tested during the implant by delivering the strongest possible CCM™ signal 20 to 30 ms longer than the LS-CCM delay with which the IPG will be ultimately programmed, as long as this delay places the CCM™ signal, including its 40 ms balancing phase, completely within the ventricular absolute refractory period, and monitoring for atrial activations. In such a case, the delay should be programmed to a longer value and lack of atrial activation confirmed. Besides proper lead location and CCM™ parameter programming, the "Atrial Tachycardia Rate" must be programmed to a sufficiently low value as a protective measure against atrial arrhythmias that could be induced by CCM™ signal delivery.

4.2 Experience and Training

Physicians who implant the OPTIMIZER Smart IPG should have experience in the implantation of pacemakers, CRT and/or implantable defibrillator devices to ensure knowledge of lead placement. Each physician implanting the OPTIMIZER Smart IPG must undergo the manufacturer's prescribed training which will be tailored to the experience of each physician.

4.3 Handling

Do not implant the OPTIMIZER Smart IPG if the package is damaged or if the device has been dropped onto a hard surface from a height of 30 cm (12 in) or more while still in the shipping box. Do not implant the device if it has been dropped onto a hard surface

after unpacking. Damaged packages or dropped devices need to be returned to Impulse Dynamics.

4.4 Storage and Handling

The recommended storage temperature range for the OPTIMIZER Smart IPG is 32°F to 104°F. Atmospheric pressure and relative humidity have no impact on the OPTIMIZER Smart IPG.

4.5 Packaging Information

The OPTIMIZER Smart IPG is supplied in a shelf box containing a literature pack and the sterile package. The sterile pack has been sterilized with ethylene oxide gas and comprises an outer TYVEK/PET blister pack containing an inner TYVEK/PET blister.

The following items are included in the shelf box:

- OPTIMIZER Smart System Insert Card
- Peel-off labels for use with implantation documents
- Sterile pack

The inner blister pack contains:

- One (1) OPTIMIZER Smart IPG
- One (1) Allen #2 torque wrench (11 oz-in = 77.68 mNm)
- One (1) Port Plug

Before opening the sterile package, check for any signs of damage suggesting that the sterility of the package or its contents might have been compromised. Damaged packages need to be returned to Impulse Dynamics. Do not attempt to resterilize the contents of the sterile package that has been damaged or in any way compromised.

4.6 Resterilization and Reuse

Do not resterilize the OPTIMIZER Smart IPG, Port Plug, or the Allen wrench provided with the device. An OPTIMIZER Smart IPG that has been explanted for any reason may not be reimplanted in another patient.

4.7 Cremation

The OPTIMIZER Smart IPG contains a sealed chemical battery and therefore must not be incinerated. Make absolutely sure to explant the device before a deceased patient is cremated.

5. CAUTIONS

5.1 Environmental Conditions

The following discussion on potential hazards from the environment focuses on maintaining the utmost patient safety. Although the OPTIMIZER Smart IPG was designed to provide the highest possible protection against such hazards, complete immunity against these risks cannot be guaranteed.

Note: The OPTIMIZER Smart IPG should not be used in the vicinity of other electrical equipment. If proper separation is not feasible, the OPTIMIZER Smart IPG has to be monitored to ensure normal function.

Just like any other IPG, the OPTIMIZER Smart IPG can be affected by interference from magnetic, electrical, and electromagnetic signals, provided these are sufficiently strong or have characteristics resembling cardiac activity. Most interference will lead to inhibition of CCM™ signal delivery. In rare cases, an interfering signal could trigger inappropriate CCM™ signal delivery. In addition, interfering signals exceeding a certain threshold may couple enough energy into the IPG to damage the IPG circuits and/or the myocardial tissue in the vicinity of the leads. The patient manual also covers these factors, and these risks should be disclosed in the discussion with the patient.

The susceptibility of a particular device is dependent on the location of the IPG pocket, the type of interfering signal, and on the programmed operating parameters.

Because of the diversity of the potential causes of electromagnetic interference, Impulse Dynamics cannot characterize and describe all sources of interference and their effects in this manual.

Warning: Patients should be instructed to be cautious in the vicinity of equipment that generates electrical or electromagnetic fields and to seek medical advice before entering an area with posted warnings advising pacemaker patients (or patients with other types of implantable devices) not to approach.

5.2 Electrocautery

Use of surgical electrocautery devices can induce CCM™ signal inhibition or can make the OPTIMIZER Smart IPG revert to its "DOWN" mode [Standby (OOO) mode, with no delivery of CCM™] with the possible loss of statistical data. The device can be damaged if high energies are coupled into the system.

Use of electrocautery in close proximity to an implanted OPTIMIZER Smart IPG can also couple radio frequency energy directly through the leads and lead tips into the cardiac muscle tissue, producing burns or possibly cardiac arrhythmias. If electrocautery is used, only brief signal bursts may be delivered and the neutral electrode has to be positioned such that the current affecting the OPTIMIZER Smart IPG and the attached leads is minimized. The risk of adverse effects can be decreased by reprogramming the OPTIMIZER Smart IPG into Standby (OOO) mode. The patient's peripheral pulse should be monitored throughout the procedure and correct operation of the OPTIMIZER Smart IPG should be verified immediately after the procedure. If the device has gone into its "DOWN" mode, it needs to be reset.

5.3 RF Ablation

RF ablation can cause the OPTIMIZER Smart IPG to inhibit CCM™ signal delivery or to revert to its "DOWN" mode [Standby (OOO) mode, with no delivery of CCM™] with the possible loss of statistical data. Depending on the amount of energy coupled into the system, the device could also be damaged. If an RF ablation procedure is performed in close proximity to the leads, the leads can couple radio frequency energy via the lead tips into the myocardium, producing burns or possibly cardiac arrhythmias.

If an RF ablation procedure has to be performed, the neutral electrode should be positioned such that the current flowing through the OPTIMIZER Smart IPG and the leads is minimized. Avoid direct contact between the ablation catheter and the OPTIMIZER Smart IPG or its leads. The risk of adverse effects can be decreased by reprogramming the OPTIMIZER Smart IPG into Standby (OOO) mode. The patient's peripheral pulse should be monitored throughout the procedure and correct operation of the OPTIMIZER Smart IPG should be verified immediately after the procedure. If the device has gone into its "DOWN" mode, it needs to be reset.

5.4 Diathermy (Medical "Short Wave" Induction Heating)

Medical diathermy is generally contraindicated in patients with implanted devices. The effects of such intense energies on the OPTIMIZER Smart IPG cannot be predicted. Although damage to the circuitry of the IPG and/or the myocardium appears unlikely, it nevertheless could occur.

If diathermy is to be used notwithstanding the contraindication, it may not be applied in proximity of the OPTIMIZER Smart IPG and its leads. The risk of adverse effects can be decreased by reprogramming the OPTIMIZER Smart IPG into Standby (OOO) mode. The patient's peripheral pulse should be monitored throughout the procedure and correct operation of the OPTIMIZER Smart IPG should be verified immediately after the procedure. If the device has gone into its "DOWN" mode, it needs to be reset.

5.5 Defibrillation and Cardioversion

Any implanted device can be damaged by external cardioversion or defibrillation. In addition, the myocardium adjacent to the lead tips and/or the tissue in the area of the device may be damaged. Altered signal thresholds could also be one of the consequences. The defibrillation current can also make the OPTIMIZER Smart IPG revert to its "DOWN" mode [Standby (OOO) mode, with no delivery of CCM™] with the possible loss of statistical data. The system can be damaged by exposure of high energies.

No particular paddle placement can avoid such damage. To decrease the risk, it is recommended to position the paddles as far away from the OPTIMIZER Smart IPG as possible. In addition, paddle positions that would bring the OPTIMIZER Smart IPG into the direct path of the defibrillation current should be avoided.

After defibrillation, the function of the OPTIMIZER Smart IPG should be closely monitored. In the unlikely event of abnormal function, lead repositioning (or replacement), reprogramming of the IPG may be required. If the device is found to have reverted to its "DOWN" mode, it needs to be reset. Internal defibrillation will not damage the device.

5.6 Radiation Therapy

Warning: Therapeutic equipment generating ionizing radiation, such as linear accelerators and cobalt machines employed for treating malignant diseases, can damage the circuits used in most active implantable devices. Because the effect is cumulative, both dose rate and total dose determine if damage will

occur and its possible extent. Please be aware of the fact that certain types of damage may not be immediately obvious. In addition, the electromagnetic fields generated by some types of radiation equipment for beam "steering" purposes can affect the function of the OPTIMIZER Smart IPG.

Radiation therapy can lead to a wide spectrum of effects, reaching from transient interference to permanent damage. It is therefore advisable to locally shield the OPTIMIZER Smart IPG against radiation if radiation therapy is to be used. During a radiation treatment and thereafter, the function of the IPG needs to be monitored. If tissue in the vicinity of the implant has to be irradiated, it may be advisable to relocate the IPG.

5.7 Nuclear Magnetic Resonance (NMR), Magnetic Resonance Imaging (MRI)

Exposure of the OPTIMIZER Smart system to strong magnetic and electromagnetic fields encountered within MRI systems has not been investigated. Even though programming the IPG into Standby (OOO) mode reduces the risk of adverse events, exposure of the patient to an MRI scan could result in:

- Unintended cardiac stimulation (induced tachycardia)
- Tissue damage near the IPG and lead electrodes with the result of inability to deliver CCM therapy
- Device malfunction (discharge of battery, damage to device electronics)

Exposure of patients with the OPTIMIZER Smart system to MRI scans should therefore not be allowed.

5.8 Lithotripsy

Warning: Direct exposure of the OPTIMIZER Smart IPG to shock waves can damage the device. A device implanted outside the shock wave path presents no clear-cut contraindication to lithotripsy. Precautionary programming of the OPTIMIZER Smart IPG to Standby (OOO) mode reduces the risk of adverse effects. The patient's peripheral pulse should be monitored during the procedure. Immediately after the treatment, the OPTIMIZER Smart IPG has to be checked for proper function. If the device is found to have reverted to its "DOWN" mode, it needs to be reset.

5.9 Therapeutic Ultrasound

Warning: Direct exposure of the OPTIMIZER Smart IPG to therapeutic ultrasound can damage the device. In addition, unexpected focusing of the ultrasound beam may harm the patient.

Therapeutic ultrasound can be used provided the implant is located far away from the ultrasound field and clearly outside the field. Precautionary programming the OPTIMIZER Smart IPG to Standby (OOO) mode reduces the risk of adverse effects. The patient's peripheral pulse should be monitored during the procedure. Immediately after the treatment, the OPTIMIZER Smart IPG should be checked for proper function. If the device is found to have reverted to its "DOWN" mode, it needs to be reset.

5.10 Transcutaneous Electrical Nerve Stimulation (TENS)

TENS is generally contraindicated in patients with implanted electrical devices. The high-voltage impulse delivered into the body by the TENS unit can impair the operation of the OPTIMIZER Smart IPG.

If a TENS unit is used nonetheless, the TENS electrodes have to be attached as far as possible from the OPTIMIZER Smart IPG and its leads. In addition, aiming for a limited current path, the TENS electrodes should be placed as close to each other as possible. The patient's peripheral pulse should be closely monitored while TENS is applied. Precautionary programming the OPTIMIZER Smart IPG to Standby (OOO) mode reduces the risk of adverse effects.

5.11 Home Appliances

Home and commercial microwave ovens do not affect the operation of the OPTIMIZER Smart IPG, provided they are in good condition and used as intended. Even microwave energy from a severely defective microwave oven directly radiating onto the IPG does not damage the device, although the sensing function may be impaired, which could eventually impact CCM™ signal delivery.

Patients with an implanted OPTIMIZER Smart IPG should be advised that some electric razors, electric power tools, and electric ignition systems, including those of gasoline powered engines, could cause interference. Generally, patients implanted with an OPTIMIZER Smart IPG may use gasoline powered engines, provided that protective hoods, shrouds, and other shielding devices have not been removed.

5.12 Store Anti-Theft Systems/Airport Security Screening Systems

Certain types of anti-theft systems, such as those installed at entrances/exits of stores, libraries and other facilities, as well as airport security systems can interfere with the OPTIMIZER Smart IPG. Such interference would most often inhibit CCM™ signal delivery. Patients should be advised to walk through such systems at a normal pace, i.e. not to slow down while passing through. Prior to passing through airport security systems, patients should notify the attendant security personnel that they carry an implant and should present their implant ID card.

5.13 Industrial Machinery

High voltage power lines, electric and arc welders, electric smelters, and power-generating equipment can interfere with the operation of the OPTIMIZER Smart IPG. For that reason, one needs to take into account the field strengths and modulation characteristics of all electromagnetic fields patients are exposed to in their workplaces or due to their lifestyle. Patients need to be specifically warned about these risks, or the OPTIMIZER Smart IPG should be programmed to minimize its susceptibility.

5.14 Transmitting Devices

Communication equipment such as radio and TV transmitters (including amateur ["ham radio"] transmitters, microwave, and CB radio transmitters with power amplifiers) as well as radar transmitters can interfere with the operation of the OPTIMIZER Smart IPG. For that reason, one needs to take into account the field strengths and modulation characteristics of all electromagnetic fields patients are exposed to in their workplaces or

due to their lifestyle. Patients need to be specifically warned about these risks, or the OPTIMIZER Smart IPG should be programmed to minimize its susceptibility.

5.15 Cellular and Mobile Phones

Cell phones and other mobile phones can affect the operation of the OPTIMIZER Smart IPG. These effects can be caused by the radio frequencies emitted by the phones or by the phones' speaker magnets. Potential effects include inhibition of or inappropriate CCM™ signal delivery if the phone is in very close proximity (within 25 cm / 10 in) of an OPTIMIZER Smart IPG and the corresponding leads. Because of the great variety of mobile phones as well as the significant physiologic differences between patients, it is impossible make generally applicable recommendations.

As a general guideline, patients implanted with an OPTIMIZER Smart IPG who would like to use a mobile phone are advised to hold the phone to the ear that is contralateral to the implant site. Patients should not carry the phone in a breast pocket or on a belt closer than 25 cm (10 in) from the implanted IPG because some phones emit signals even when they are turned on but not in use.

Compared to smaller cell phones, portable (handbag) and mobile (permanent car or boat installation) phones will generally transmit at higher power levels. For phones with higher transmission power levels, it is recommended to maintain a minimum separation of 50 cm (20 in) between the antenna and the implanted IPG.

6. POTENTIAL ADVERSE EFFECTS

Examples of adverse effects that may occur as the result of the surgical procedure are listed below in the order of their clinical severity:

1. Death
2. Arrhythmias (brady- or tachyarrhythmias including fibrillation)
3. Stroke or TIA ("transient ischemic attack")
4. Respiratory/ventilatory failure
5. RA/RV perforation
6. Hemorrhage
7. Infection
8. Pleura or pericardial effusion
9. Pneumothorax

Examples of additional adverse effects potentially occurring secondary to CCM™ signal delivery are listed in the table below in the order of their clinical severity:

1. Abnormal cardiac function
2. Atrial and Ventricular Tachyarrhythmias
3. Atrial and Ventricular Bradyarrhythmias
4. Worsening heart failure

5. Myocardial tissue damage
6. Chest pain

7. DEVICE IMPLANTATION

7.1 General Considerations

Generally, the OPTIMIZER Smart IPG is implanted in the right pectoral region. Subclavian venous access is preferred over access via the axillary or cephalic vein. Two right ventricular leads are placed for CCM™ signal delivery, one of these preferably in an anterior septal and the other in a posterior septal location, approximately half way between base and apex. Placing both leads in an anterior or posterior septal location is an acceptable alternative, provided the leads are separated by at least 2 cm. In patients who carry an ICD, one needs to ensure that there is adequate separation between CCM™ leads and ICD lead.

Warning: Avoid Subclavian crush by proper lead placement. Patients need to be monitored closely after the implantation procedure.

Warning: Exercise care while placing the leads to avoid swelling of the steroid plug or formation of a blood clot, which could prevent retraction of the corkscrew.

Warning: It is important to avoid prolonged manipulation of the leads and catheters in the venous system, which could lead to venous thrombosis.

Warning: During implantation, leads and catheters need to be manipulated with extra caution in order to avoid perforation of the right ventricular wall. Obtain X-rays, perform echocardiography, and device interrogation after implantation to detect perforations even in the absence of corresponding symptoms.

Warning: In order to prevent vascular injury and hemorrhage, be extremely cautious when introducing catheters and leads into arteries and veins.

7.2 Opening the Lead Sterile Package(s)

Visually inspect the lead packages before opening them for implantation. Follow the instructions provided by the lead manufacturer. Unless otherwise indicated by the lead manufacturer, proceed as follows with each sterile package:

- Open the shelf box outside the sterile field and remove the TYVEK/PET molded tray.
- Using the provided tab, peel back the TYVEK from the outer PET molded tray, taking care not to touch the inner sterile package.
- Using strict sterile technique, open the inner sterile blister pack and make it accessible to the scrub nurse. At the recess adjacent to the molded tab, the inner TYVEK/PET container can be removed from the outer tray with a pair of forceps.
- Peel back the inner cover starting at the provided peel tab.
- Remove the lead from the inner package and place it on a sterile and lint-free surface.

7.3 Opening the OPTIMIZER Smart Sterile Package

The OPTIMIZER Smart IPG is supplied in a shelf box that contains a literature pack and the sterile package sterilized with ethylene oxide gas. The sterile package comprises an outer TYVEK/PET blister pack containing an inner TYVEK/PET blister. Visually inspect the package before opening it for the implantation procedure. Please contact your Impulse Dynamics representative if package or seal is damaged. The inner blister pack contains:

- One (1) OPTIMIZER Smart IPG
- One (1) Allen #2 torque wrench (11 oz-in = 77.68 mNm)
- One (1) Port Plug

Open the shelf box outside the sterile field and remove the TYVEK/PET molded insert. To open the sterile package, proceed as follows:

- Starting at the provided tab, peel back the TYVEK from the outer PET molded insert, taking care not to touch the sterile inner package.
- Maintaining strict sterile technique, make the inner sterile blister pack accessible to the scrub nurse. The inner TYVEK/PET container can be removed from the outer tray with a pair of forceps inserted at the recess next to the molded tab.
- Peel back the inner cover starting at the provided tab.
- Remove the OPTIMIZER Smart IPG and the accessories.

7.4 Verifying Lead Placement

Note: The Programmer Wand of the OMNI Smart Programmer is not sterile and cannot be sterilized. The Programmer Wand needs to be placed in a sterile cover before it can be brought into the sterile field.

Place the Programmer Wand over the IPG. Ask the person operating the Programmer (outside the sterile field) to measure the lead impedances and make sure they are adequate.

Note: Any significant lead impedance deviation at a subsequent check-up may be a sign of lead displacement or indicative of another problem requiring further investigation.

Once the leads are in place, secure each lead to its respective lead anchor sleeve. Clean the lead body with sterile saline before you secure the anchoring sleeve to the lead. Secure the anchoring sleeve with two non-absorbable ligatures and tighten gently -- **Do Not Over-Tighten**.

7.5 Connecting the Implanted Leads to the OPTIMIZER Smart IPG

Important considerations:

- When tightening or loosening the set screws, always insert the tip of the torque wrench fully and in line with the set screw. Do not insert the wrench into the set screw at an angle.

- Prior to inserting the IS-1-BI lead connectors, verify visually that none of the set screws protrude into any of the IPG header cavities (please refer to the diagram on the IPG). Back off any set screw found protruding beyond the wall into the header cavity by turning it back with the Allen wrench in a counter-clockwise direction. Turn the set screw just enough so that its tip is no longer inside the header cavity. Do not back the set screw completely out of the terminal block.
- Under no circumstances may items other than the implantable lead connectors be introduced into the port of the IPG connector terminal.

Note: Provided the connectors are correctly installed, the connector retention force in the terminals is at least 10 N.

Clean the lead plugs with sterile distilled water (if using saline, wipe the plugs dry with a surgical sponge afterwards) and fully insert each plug into the respective connector terminal at the IPG. Observe that the male ends of the lead plugs are inserted beyond the respective lead tip terminals. Tighten the set screws using the sterile #2 Allen torque wrench included in the IPG package. Turn the torque wrench clockwise until there is a distinct clicking sound/feel. This feature prevents over-tightening of the set screw. Carefully apply traction on the strain relief of each lead to make sure that the leads are securely anchored in the terminal. Finally, tighten the set screws securing the contact between the rings of the plugs and the corresponding parts of the terminal block.

Insert the Port Plug provided with the OPTIMIZER Smart IPG package into the "A" port of the IPG and gently tighten the ring set screw only. The protruding length of the Port Plug may be shortened, but it is recommended to leave at least 1 cm length protruding from the IPG to enable future removal of the Port Plug if it becomes necessary to connect an atrial sensing lead.

Warning: DO NOT tighten the tip set screw or damage to the Port Plug may occur!

Note: Alternately, any commercially available bipolar IS-1 port plug may be used to plug the atrial port of the OPTIMIZER Smart IPG.

7.6 Dissection of the IPG Pocket

Blunt dissection directly on top of the fascia is the preferred method for creating the pocket, which should be just large enough to accommodate the IPG and any loops of excess lead.

Note: When dissecting the pocket, please bear in mind that for charging to be possible, the distance between charging wand and OPTIMIZER Smart IPG must not exceed 4 cm (1.5 in).

Before tightening the set screws, please ensure that the connector pin of each lead is completely inserted into the corresponding connector terminal of the OPTIMIZER Smart IPG.

7.7 Inserting the OPTIMIZER Smart IPG and Closing the Pocket

Insert the OPTIMIZER Smart IPG into the subcutaneous pocket. Although the OPTIMIZER Smart IPG can theoretically be interrogated and charged in any position,

the preferred placement is such that the lettering points to the front, which provides the best link between the charging coil inside the header and the OPTIMIZER Mini Charger.

The recommended maximum depth of implant for proper device interrogation and charging is not more than 2.5 cm. Coil any excess lead and place these coils around the IPG or in the pocket inferior to the device. Ensure that the leads form not more than a gentle curve where they exit the IPG connector terminal and that they are not under traction or strain. Secure the IPG to the fascia with a non-absorbable suture and close the pocket.

Radiographs should be obtained after device implantation to rule out pneumothorax, even if there are no symptoms. In addition, proper device function should be verified by device interrogation, which can also detect lead displacement. Thereafter, patients should receive standard post-operative care for a minimum of 24 hours prior to discharge. The use of narcotics for pain relief should be minimized.

Remark: If the patient is also implanted with an ICD, concomitant device interaction testing should be performed (see Appendix III).

8. DEVICE EXPLANTATION / REPLACEMENT

Special care should be exercised when opening the IPG pocket so as to not damage the leads implanted with the OPTIMIZER Smart IPG. Once the IPG is lifted out of the pocket, the set screws can be loosened with a sterile #2 Allen wrench. While holding the IPG in one hand, grasp each silicone lead connector between thumb and forefinger. Pull the lead connectors from the terminal by cautious application of constant traction. Grasping the plugs with a sterile pad can help improve traction. Never apply traction to the actual lead body, which could damage the leads and cause lead failure.

Note:

- When tightening or loosening a set screw, always insert the tip of the torque wrench fully into and in line with the set screw. Do not insert the torque wrench into the set screw at an angle.
- Prior to inserting the IS-1-BI lead connectors, verify visually that none of the set screws protrudes into any of the IPG header cavities. Back off any set screw found protruding beyond the wall into the header cavity by turning it back in a counter-clockwise direction with the Allen wrench. Turn the set screw just enough so that its tip is no longer inside the header cavity. Do not back the set screw completely out of the terminal block.

Clean the lead plugs with sterile distilled water (if using saline, wipe the plugs dry with a surgical sponge afterwards) and fully insert the plug into the respective connector terminal of the OPTIMIZER Smart IPG. Observe that the tips of the lead plugs are inserted beyond the respective lead tip terminals. Tighten the set screws using the sterile #2 torque wrench included in the OPTIMIZER Smart package. Turn the Allen wrench clockwise until you can clearly hear and feel the clicking that limits excessive torque on the set screw. Carefully apply traction to the strain relief of each lead to make sure that the leads are securely anchored in the terminal. Finally, tighten the set screws securing the contact between the rings of the plugs and the corresponding parts of the terminal block.

Make sure to visually verify that the lead insulation is intact when replacing an OPTIMIZER Smart IPG. At this time, the impedances and sensing thresholds should also be assessed with a PSA.

When the OPTIMIZER Smart IPG is being explanted and not replaced, the remaining implanted leads need to be capped after they are disconnected from the IPG.

All explanted OPTIMIZER Smart IPGs should be returned to Impulse Dynamics for testing and analysis, which can provide valuable information on how to further improve device quality and reliability.

Warning: Never incinerate an OPTIMIZER Smart IPG. The IPG must be explanted before a deceased patient is cremated.

Warning: Implantable parts are not to be reused if they have previously been implanted in another patient.

9. OPTIMIZER SMART IPG: FUNCTIONS AND PROGRAMMING OPTIONS

9.1 Operating Modes

The implantable OPTIMIZER Smart IPG features three operating modes:

- Standby (OOO): The device is in standby; no events are sensed and no CCM™ signal trains are delivered.
- Active ODO-LS-CCM: The device senses atrial, ventricular, and local sense events and is capable of CCM™ signal delivery.
- Active OVO-LS-CCM: The device senses ventricular and local sense events and is capable of CCM™ signal delivery without the need for the detection of atrial sense events.

9.2 CCM™ Off Status

Under certain conditions, which are listed below, the OPTIMIZER Smart IPG is set to a special "Off" status:

- **Permanent Off:** In this state, the OPTIMIZER Smart IPG does not deliver CCM™ signals, although it senses and classifies cardiac events. This status can only be changed by using the OMNI Smart Programmer software to reprogram the OPTIMIZER Smart IPG under supervision of a physician. The patient or a physician can force the OPTIMIZER Smart IPG into the **Permanent Off** state by placing a magnet over the implant site of the OPTIMIZER Smart IPG and by maintaining it in close proximity to the device for at least two cardiac cycles (2 - 3 seconds).

  Note: This **Permanent Off** state is maintained even after the magnet is removed from the implant site.

- **DOWN:** In this state, the OPTIMIZER Smart IPG does not deliver CCM™ signals, and it may not sense cardiac events. Reversal of this state can only be accomplished by resetting the OPTIMIZER Smart IPG with the OMNI Smart Programmer software under physician supervision. In the unlikely event of

inconsistent operation of the system's logic circuits, the OPTIMIZER Smart IPG will automatically assume the "**DOWN"** state.

9.3 A/V Sensing

Through leads implanted in the heart, the OPTIMIZER Smart IPG can sense, detect, and analyze activity in the form of electrical signals generated by the heart, for example, electrical depolarization events which occur during the cardiac cycle. The controller and signal generation circuitry of the OPTIMIZER Smart IPG are programmed to receive the signals detected by electrodes and sensing circuitry and, based on the detected signal, analyze their characteristics (including, for example, magnitude and timing), and to determine whether or not to trigger the delivery of the CCM™ signal, as well as when to deliver the CCM™ signal.

9.3.1 A/V Sensing Leads

Right heart events are detected throughone sensing lead:

- **V lead:** lead positioned in the right ventricle (V)

9.3.2 A/V Sensing Parameters

A and V polarity and sensitivity are the parameters determining how right heart events are sensed.

- **Sensitivity:** With the OMNI Smart Programmer software, the Ventricle sensitivity to set to any one of 18 values between 0.1 mV and 10.0 mV.

  Note: When the OPTIMIZER Smart IPG is in Active OVO-LS-CCM mode, the minimum allowable setting for the Ventricle sensitivity is 1.0 mV.

- **Polarity:** To configure V sensing, the OPTIMIZER Smart IPG provides the following options:
  - **Bipolar:** The signal between lead "tip" (distal electrode) and "ring" (proximal electrode) of a bipolar lead is sensed.
  - **Unipolar:** The signal between lead tip (distal electrode) and the case of the OPTIMIZER Smart IPG is sensed.

9.3.3 Refractory Period

The Refractory period is the time interval when the OPTIMIZER Smart IPG does not detect input events. The refractory period is applicable to the right heart sensing:

- **Refractory:** Signals sensed within this period after an atrial or ventricular event do not register as atrial or ventricular events. With the OMNI Smart Programmer software, the A/V refractory period can be set to values between 148 ms and 453 ms, in 8 ms increments.

9.4 CCM™ Delivery Options

The implantable OPTIMIZER Smart IPG features three CCM™ delivery scheduling options:

- **CCM OFF:** No CCM™ signal delivery
- **Timed:** The device is programmed to deliver cardiac contractility modulation therapy within the time frame between Start Time (default: 0:00) and End Time (default: 23:59). The default configuration in the USA is for 1 hour ON Time followed by 3:48 hours OFF Time, repeatedly, to produce 5 hours of programmed cardiac contractility modulation therapy per day.

  Note: An ON phase is started after each charging process. The timer will resume the normal program on the following midnight.
- **Continuous:** Continuous CCM™ signal delivery (for testing purposes only)

9.5 CCM™ Signal Delivery

This section describes how the implantable OPTIMIZER Smart IPG delivers CCM™ signals to the cardiac tissue during the absolute refractory period.

9.5.1 Channels

CCM™ signals that are generated by the signal generation circuitry of the OPTIMIZER Smart IPG can either be delivered through one of the following channels or through a combination of these channels:

- **V lead**
- **LS lead**

9.5.2 CCM™ Signal Parameters

The CCM™ signal is a pulse train comprising a programmable number of consecutive pulses, each with two phases of opposite polarity and programmable duration.

- **Number of Pulses:** With the OMNI Smart Programmer software, the number of pulses can be set to 1, 2, or 3.
- **Delay:** CCM™ signal delivery is triggered by the Local Sense event. The delay parameter (coupling interval) is the time interval between the leading edge of the Local Sense triggering event and the start of CCM™ pulse train delivery. With the OMNI Smart Programmer software, the delay parameter can be set to values between 3 ms and 140 ms, in 1 ms increments. This delay range is designed to ensure that the delivery is only within the absolute refractory period, and to avoid potential excitatory behavior of the CCM™ signal.

  Note: When the OPTIMIZER Smart IPG is in Active OVO-LS-CCM mode, the maximum allowable setting for this parameter is 45 ms.
- **Amplitude (Magnitude):** This is the initial voltage of the CCM™ signal. With the OMNI Smart Programmer software, the amplitude can be set to values between 4.0 V and 7.5 V, in 0.5 V increments.
- **Phase Duration:** The phase duration of the pulses comprising the CCM™ signal can be programmed with the OMNI Smart Programmer software to

one of 4 possible values between 5.14 ms and 6.60 ms. The duration of both phases are automatically set to identical values.

- **Phase Polarity:** The phase polarity of the pulses comprising the CCM™ signal can be programmed with the OMNI Smart Programmer software to "Positive" or "Negative". When the polarity of PHASE 1 is set to one value, the polarity of PHASE 2 is automatically set to the opposite value

9.5.3 Balancing Phase

Delivery of each CCM™ pulse train is completed by a Balancing Phase, which discharges any residual polarization at the electrode/tissue interface. Balancing is accomplished by short-circuiting the channels used to deliver the CCM™ signal for a period of 40 ms.

9.5.4 Parameter Interaction

In order to avoid false event detections, the CCM™ signal has to be delivered entirely within the right atrial and right ventricular refractory period. Prior to the end of these refractory periods, an 86 ms long noise window is activated to detect external interference. Therefore, CCM™ signal delivery has to be completed before the noise window is opened. This is accomplished with the following constraint:

- *The sum of the values Alert Start, Alert Width, CCM™ Delay, and CCM™ Train Total Duration must be smaller than the lower of the following two values: right atrial refractory period, right ventricular refractory period minus 86 ms.*

If the V channel is used for CCM™ signal delivery, the balancing phase also needs to be completed before the noise window starts. This can be guaranteed by the following constraint:

- *If the V channel is used for CCM™ signal delivery, the sum of the values Alert Start, Alert Width, CCM™ Delay, CCM™ Train Total Duration, and Balancing Phase (40 ms) needs to be smaller than the lower of the following two values: right atrial refractory period, right ventricular refractory period minus 86 ms.*

The Alert Start time relates to the right ventricular event. Thus, if the Alert Start value is negative and if a local sense event is detected during the AV interval, a right ventricular event will have to occur and be detected before the device can determine if the event fell inside the alert window. That implies that the OPTIMIZER Smart IPG cannot deliver a CCM™ signal prior to the right ventricular event occurring. This is asserted by the following constraint:

- *The sum of Alert Start and CCM™ Delay must be equal to or greater than 3 ms*

9.6 CCM™ Inhibit Parameters

By analyzing the train of sensed cardiac events based on their succession and their temporal order, the OPTIMIZER Smart IPG "decides" for each heart action whether to deliver CCM™ signals or not.

9.6.1 Number of Beats for CCM Inhibition

For the period when CCM™ signal delivery is inhibited, one can program the number of beats for which CCM™ signal delivery will continue to be inhibited after the initial inhibiting event. With the OMNI Smart Programmer software, the total number of inhibited beats can be set to any value between 1 and 16. This means that CCM™ delivery can be inhibited from to none to 15 additional beats beyond the beat leading to the initial inhibiting event.

Please note that this number of inhibited cycles applies to the most current event leading to signal inhibition, i.e. a new inhibiting condition occurring during a period of already inhibited CCM™ signal delivery will start a new inhibition period.

9.6.2 Conditions Causing Inhibition in Active OVO-LS-CCM Mode

The following cardiac activities or events are sensed and detected by the OPTIMIZER Smart IPG while it is in its **Active** state. These events are also entered into the statistical data set, and they pertain to transmitted marker events. When CCM™ train delivery is on, such events inhibit CCM™ signal delivery. An event that occurs outside the configurable time window(s) could indicate, for example, suspected cardiac arrhythmia, and, in response to detecting the suspected arrhythmia, or other abnormal event, the CCM™ signal would not be delivered.

- **LS Out of Alert:** A local sense event detected after the end of the Local Sense Alert Window triggers an LS Out of Alert condition. The Local Sense Alert Window is the time interval during which the leading edge of valid LS events triggers CCM™ signal delivery. How this is programmed is detailed in Section 9.8.1.
- **Ventricular Tachycardia (VT):** Any ventricular rate exceeding a certain threshold is considered ventricular tachycardia. Using the OMNI Smart Programmer software, the ventricular tachycardia threshold rate can be set to one of 19 possible values between 62 bpm and 110 bpm. CCM signal delivery is *always inhibited* when ventricular tachycardia is detected.
- **Ventricular noise:** Despite various methods for detecting and filtering noisy signals implemented in the OPTIMIZER Smart IPG, noise from powerful electromagnetic sources (e.g. from portable telephones, radio transmitters, etc.) as well as noise from physiological events (e.g. myopotentials, etc.) can interfere with the detection of cardiac events.

  Any time higher rate signals (greater than 11.6 Hz) are detected on the atrial or ventricular channel, the control logic of the OPTIMIZER Smart IPG assumes the presence of noise and declares an A/V noise condition. CCM™ signal delivery is *always inhibited* if atrial or ventricular noise is detected.

9.7 Local Sensing

The local electrical activity of the ventricular myocardium is detected via the Local Sense (LS) lead. LS channel sensitivity can be set with the OMNI Smart Programmer software to one of 18 values between 0.1 mV and 10.0 mV.

Note: When the OPTIMIZER Smart IPG is in Active OVO-LS-CCM mode, the minimum allowable setting for this parameter is 1.0 mV.

9.8 CCM™ Triggering Based on Local-Sense Events

Delivery of CCM™ signal trains is synchronized with the intrinsic myocardial electrical activity in the vicinity of the Local Sense (LS) electrode. The LS channel is configured to sense the electrical activity of a small, localized area of the heart (near the fixation site of the LS electrode). In response to this sensed activity, the OPTIMIZER Smart IPG evaluates the myocardial electrical signal to determine whether it meets the criteria defined by the set of LS parameter values programmed into the device. If the criteria are met, then the device delivers the CCM™ stimulus. The timing of the signal detected through the LS channel within a cardiac cycle, especially with regard to the R wave, is the main criterion for the OPTIMIZER Smart IPG to classify the cycle as normal or abnormal. CCM™ signals are *not delivered* during cycles classified as abnormal.

Provided that the CCM™ signal delivery is not prohibited by detecting a Local Sense event inconsistent with the Alert Window, the OPTIMIZER Smart IPG may deliver CCM pulses to thousands of heart beats over the course of a day. For example, it may deliver CCM™ to several thousand beats out of 50,000 consecutive beats, taking into account any conditions causing inhibition (as noted in Section 9.6.2) that result in CCM™ pulses not being delivered.

9.8.1 Local Sense Alert Window

When the internal logic of the device detects ventricular events corresponding to cardiac cycles not classified as abnormal because of noise, atrial tachycardia, or suspected PVCs, it will open a Local Sense Alert Window. The Alert Window can be inside the AV interval, inside the VA interval, or partially inside the AV and partially inside the VA interval.

The first event detected within the window serves as a trigger for CCM™ signal delivery.

Valid Local Sense events detected outside the Alert Window are considered to be PVCs and inhibit CCM™ signal delivery for a programmable number of cycles. Inhibiting Local Sense events can be detected even between a triggering Local Sense event and the start of the corresponding CCM™ signal, which in this case will not be delivered.

The Local Sense Alert Window is the time interval during which the leading-edge of valid LS events is used to trigger CCM™ signal delivery.

The position in time of this window is determined by two programmable parameters:

- **Alert Start:** Begins with the right ventricular event. Using the OMNI Smart Programmer software, Alert Start can be set to values between -100 ms and 100 ms, in 2 ms increments. Please note that the Alert Window starts inside the AV interval if this value is negative.
- **Alert Width:** Equivalent to the duration of the Alert Window. Using the OMNI Smart Programmer software, Alert Width can be set to values between 1 ms and 40 ms, in 1 ms increments. If the sum of **Alert Start** and **Alert Width** is negative, the Alert Window ends inside the AV interval.

  Note: When the OPTIMIZER Smart IPG is in Active OVO-LS-CCM mode, the maximum allowable setting for this parameter is 30 ms.

The leading edge of the first event detected within this window is used to trigger CCM™ signal delivery. When an event is detected, the Local Sense Alert Window is immediately closed. Any Local Sense events detected after the window closes are considered to lie outside the Alert Window and lead to the **LS Out of Alert Status**.

If a Local Sense event is detected outside the Alert Window, CCM™ signal delivery is *always inhibited.*

9.8.2 Local Sense Refractory Periods in Active OVO-LS-CCM Mode

With the exception of events occurring during the Local Sense Refractory Periods, any event detected through the LS channel is considered a valid Local Sense event.

Local Sense Refractory Periods include:

- **Pre V Refractory Period:** Ends with the ventricular event. With the OMNI Smart Programmer software, the duration can be set to values between 0 ms and 55 ms, in 5 ms increments.
- **Post V Refractory Period:** Begins with the ventricular event. With the OMNI Smart Programmer software, the duration can be set to values between 0 ms and 39 ms, in 1 ms increments.
- **Post LS Refractory Period:** Begins with a valid LS event. With the OMNI Smart Programmer software, the duration can be set to one of 56 possible values between 15 ms and 250 ms.
- **Post CCM Refractory Period:** Begins with the start of the CCM™ signal train and ends with the end of the **Right V Refractory Period.**

9.8.3 Remarks

If the Pre- and Post-ventricular LS Refractory Periods are inside the Local Sense Alert Window (i.e. if the Alert Start is negative and the sum of Alert Start and Alert Width is longer than the Post-Ventricular Refractory Period), only Local Sense events falling inside the Alert Window and outside the Ventricular LS Refractory Periods will trigger CCM™ signal delivery.

If a Local Sense event is detected after the window closes and before CCM™ signal train delivery commences, the new event is considered to be outside the Alert Window and CCM™ signal delivery will be inhibited.

In Active ODO-LS-CCM mode, the Local Sense Alert Window cannot start prior to the atrial event. Therefore, if the Alert Start occurs before the end of the post-atrial refractory period (Alert Start is negative and the AV interval minus the Post-Atrial Refractory Period is smaller than the absolute value of Alert Start), the Local Sense Alert Window will start at the end of the Post-Atrial Refractory Period.

9.8.4 Parameter Interaction

Local Sense signals are ignored during Local Sense refractory periods. Therefore, the OMNI Smart Programmer software will not permit the *Alert Window to start or end inside the pre- and/or post-ventricular refractory period.*

10. SERVICE AND WARRANTY

For emergency assistance, Impulse Dynamics has professional technical staff on call around the clock. If you require assistance, please contact your local Impulse Dynamics representative.

10.1 Limited Warranty Information

Impulse Dynamics warrants that all IPGs (including the respective firmware and software) will be free from defects in workmanship and materials for a period of 24 months after the original implantation of the IPG, unless a longer period is required pursuant to applicable law (the "Warranty Period").

If it appears that any IPG or part thereof appears to be defective in workmanship or materials, or fails to conform to applicable specifications, Impulse Dynamics shall either replace defective or non-conforming implantable components or repair or replace defective or non-conforming non-implantable components. The warranty period for a replaced or repaired IPG shall be the time remaining on the original warranty period or nine months from delivery of the repaired or replaced IPG, whichever is longer.

Under this warranty, Impulse Dynamics shall not be liable if tests and analyses reveal that the alleged defect or non-conformity of the IPG is not present or was caused by improper use, neglect, improper implantation, or follow-up, unauthorized repair attempts by the user, or due to accident, fire, lightning, or other hazards.

10.2 Mandatory Battery Charging

The rechargeable battery in the OPTIMIZER Smart IPG is designed to provide optimal performance if it is completely recharged on a weekly basis. While letting more than one week lapse between full charging cycles is acceptable if it occurs infrequently, regular weekly recharging sessions are required to prevent battery deterioration, which would ultimately decrease device longevity.

THIS PAGE INTENTIONALLY LEFT BLANK

APPENDIX I

As a convenience to the user, the following overview provides a brief and succinct summary of the characteristics of the OPTIMIZER Smart IPG. Some of these data are also presented in the manual in text form.

Physical Characteristics

Model	OPTIMIZER Smart IPG
Height (mm)	69.4 ± 2.0
Width (mm)	47.5 ± 0.5
Thickness (mm)	11.5 ± 0.5
Volume (cm^3)	30.5 ± 0.5
Mass (g)	46 ± 3.0
Area of exposed metal can (cm^2)	58.1
Radiopaque ID	**ID OS y**[1]
Materials in contact with human tissue	Titanium Epoxy resin Silicone rubber
Lead connectors	3.2 mm; IS-1/VS-1
[1]The manufacturer code stands for Impulse Dynamics; the model ID code for the OPTIMIZER is "OS"; y corresponds to the year code: A for 2015, B for 2016, C for 2017, D for 2018 etc…	

Battery

Model and IEC type	QL02001, rechargeable
Manufacturer	Quallion
Chemistry	Lithium-ion
Low battery indicator	3.3 V
Battery life to end of service	>15 years[1]
Approximate capacity after recharging to LBI	200 mAh

[1] Replacement indicated when the IPG can no longer maintain the delivery of CCM therapy for a full week with routine weekly charging.

Current Consumption

Mode	Current
OOO	Less than 40 µA
ODO-LS - CCM OFF	Less than 45 µA
ODO-LS - CCM ON	Less than 1200 µA[1]

[1]Current consumption of the OPTIMIZER Smart IPG is strongly dependent on the energy delivered by the CCM™ pulse train.

Safe Mode

Mode	Description
DOWN mode	When the device encounters conditions considered to be the result of faulty device circuitry or software, it will switch to DOWN mode. In DOWN mode, the device is completely quiescent; CCM signals are not delivered and cardiac events are not sensed. To take the device out of this mode, a device reset must be performed under physician supervision.

Programmable Parameters

OPERATING MODES

Mode	Characteristics
OOO	Standby mode: no events are sensed and no CCM™ impulse trains are delivered
ODO-LS-CCM	Active mode where the device senses atrial, ventricular and Local Sense events and is capable of CCM™ signal delivery
OVO-LS-CCM	Active mode where the device senses ventricular and local sense events and is capable of CCM signal delivery without the need for the detection of atrial sense events.

A /V SENSING PARAMETERS

Parameter Name	Values
Ventricle sense amplifier sensitivity	18 possible between 0.1 mV to 10.0 mV
Ventricle sensing polarity	Unipolar, Bipolar
Ventricle refractory period	Between 148 ms to 453 ms in 8 ms increments

CCM™ TRAIN PARAMETERS

Parameters Name	Values	
CCM Mode	CCM OFF	No pulse train enabled
	Timed	As defined by the parameter values programmed under the CCM Scheduling Tab.
	Continuous	The pulse train is enabled for the entire day.
Number of Pulses	1, 2, or 3	
CCM™ Train Delay	Between 3 ms and 140 ms in 1 ms increments	
CCM™ Pulse Amplitude	Between 4.0 V and 7.5 V in 0.5 V increments	
CCM™ Delivery Channels	LS and/or V	
Phase 1 Duration	4 possible between 5.14 ms and 6.60 ms.	
Phase 1 Polarity	"Positive" or "Negative".	

CCM™ INHIBIT PARAMETERS

Parameter Name	Values
Count	Between 1 and 16 in increments of 1
Ventricular Tachycardia Rate[1]	19 possible between 62 bpm and 110 bpm

[1]: Active only when the OPTIMIZER Smart IPG is in Active OVO-LS-CCM mode.

LOCAL SENSE PARAMETER

Parameter Name	Values
Local Sense Sensitivity	18 possible between 0.1 mV to 10.0 mV
Local Sense Alert Start	Between –100 ms to 100 ms in 2 ms increments
Local Sense Alert Width	Between 1 ms to 40 ms in 1 ms increments
Local Sense Pre-Ventricular refractory period	Between 0 ms to 55 ms in 5 ms increments
Local Sense Post-Ventricular refractory period	Between 0 ms to 39 ms in 1 ms increments
Local Sense Post-LS refractory period	Between 15 ms to 25 ms in 1 ms increments and between 25 ms and 250 ms in 5 ms increments

Factory Settings

PARAMETERS RELATED TO CONTROLLING RIGHT HEART SENSING

Mode	OOO
Atrial Sense Amplifier Sensitivity	1.3 mV
Ventricular Sense Amplifier Sensitivity	2.0 mV
Ventricular Sensing Polarity	Bipolar
Atrial Sensing Polarity	Bipolar
Ventricular Refractory Period	250 ms
Post-Ventricular Atrial Refractory Period	250 ms

CCM™ PULSE TRAIN ACTIVATION

CCM™ Pulse train enable	OFF

CCM™ PULSE TRAIN TIMING

Number of pulses	2
Train delay	35 ms
Phase 1 duration	5.14 ms
Phase 2 duration	5.14 ms
Phase 1 polarity	Positive
Phase 2 polarity	Negative
CCM™ Pulse Amplitude	7.5 V
CCM™ signal delivery channel	LS, V
Interval	0 ms

CCM™ INHIBIT ALGORITHM

CCM™ Inhibit Count	2 beats
Short AV Delay	70 ms
Long AV Delay	398 ms
Atrial tachycardia rate	154 bpm

LS CHANNEL PROGRAMMABLE PARAMETERS

LS Sensitivity	2.0 mV
LS Alert Window Start	-10 ms
LS Alert Window Width	30 ms
LS Pre-Atrial LS Refractory Period	5 ms
LS Post-Atrial LS Refractory Period	5 ms
LS Pre-Ventricular LS Refractory Period	0 ms
LS Post-Ventricular LS Refractory Period	0 ms
LS Post-LS Refractory Period	20 ms

CCM™ SCHEDULE PARAMETERS[1]

Start time	00:00
End time	23:59
On Time	01:00
Off Time	02:25

[1] Setting values are for CCM™ delivery of 7 hours per day. The FDA approved dosage is 5 hours per day.

CHARGER ALARM PARAMETERS

Minimum Target % for CCM™ Delivery	30%
Maximum Lead Displacement	20%

Emergency Programming

PARAMETERS RELATED TO CONTROLLING RIGHT HEART SENSING

Mode	OOO
Atrial Sense Amplifier Sensitivity	1.3 mV
Ventricular Sense Amplifier Sensitivity	2.0 mV
Ventricular Sensing Polarity	Bipolar
Atrial Sensing Polarity	Bipolar
Ventricular Refractory Period	250 ms
Post-Ventricular Atrial Refractory Period	250 ms

CCM™ PULSE TRAIN ACTIVATION

CCM™ Pulse train enable	OFF

CCM™ PULSE TRAIN TIMING

Number of pulses	2

Train delay	35 ms
Phase 1 duration	5.14 ms
Phase 2 duration	5.14 ms
Phase 1 polarity	Positive
Phase 2 polarity	Negative
CCM™ Pulse Amplitude	7.5 V
CCM™ signal delivery channel	LS, V
Interval	0 ms

CCM™ INHIBIT ALGORITHM

Programmable parameters to inhibit CCM™ signal delivery	
CCM™ Inhibit Count	2 beats
Short AV Delay	70 ms
Long AV Delay	398 ms
Atrial tachycardia rate	154 bpm

LS CHANNEL PROGRAMMABLE PARAMETERS

LS Sensitivity	2.0 mV
LS Alert Window Start	-10 ms
LS Alert Window Width	30 ms
LS Pre-Atrial LS Refractory Period	5 ms
LS Post-Atrial LS Refractory Period	5 ms
LS Pre-Ventricular LS Refractory Period	0 ms
LS Post-Ventricular LS Refractory Period	0 ms
LS Post-LS Refractory Period	20 ms

CCM™ SCHEDULE PARAMETERS[1]

Start time	00:00
End time	23:59
On Time	01:00
Off Time	02:25

[1] Setting values are for CCM™ delivery of 7 hours per day. The FDA approved dosage is 5 hours per day.

CHARGER ALARM PARAMETERS

Minimum Target % for CCM™ Delivery	30%
Maximum Lead Displacement	20%

APPENDIX II

Communications/Telemetry

Between the OPTIMIZER Smart IPG and the OMNI Smart Programmer:

- **OPTIMIZER Smart IPG to OMNI Smart Programmer:**
  - PPM: "0" = 180 µs, "1" = 270 µs
  - 14.5 kHz LC excited by pulse
  - 1 cycle per pulse until dampened to 10%
  - Energy invested per pulse 0.36 µJ → 5.14 mW_{peak} per pulse; 1.8 $mW_{average}$
- **OMNI Smart Programmer to OPTIMIZER Smart IPG:**
  - AM: "0" = no carrier, "1" = carrier for 305 µs
  - 23 kHz carrier frequency
  - Power: 0.56 W_{peak}; 0.27 $W_{average}$

APPENDIX III

Testing procedure for device/device interaction:

Patients with a concomitant device (e.g. ICD, pacemaker) require additional testing at the end of the implant procedure to ensure appropriate function of both the OPTIMIZER Smart IPG and the concomitant device. The steps of the required testing procedure are as follows:

1. Program the ICD so that it does not deliver antitachycardic therapy during this test.
2. Program the sensing windows of the OPTIMIZER Smart IPG and verify that it can be programmed to consistently delivery cardiac contractility modulation therapy in the presence of the concomitant device.
3. Activate cardiac contractility modulation therapy and analyze the real-time intracardiac electrograms and marker channels to ensure that the cardiac contractility modulation therapy does not cause inappropriate oversensing during normal sinus rhythm which cannot be resolved by reprogramming or lead repositioning.
4. Activate cardiac contractility modulation therapy and analyze the real-time intracardiac electrograms and marker channels to ensure that the cardiac contractility modulation therapy does not cause inappropriate undersensing during normal sinus rhythm which cannot be resolved by reprogramming or lead repositioning.
5. Activate cardiac contractility modulation therapy in patients requiring antibradycardic pacing and analyze the intracardiac electrograms and marker channels to ensure that the cardiac contractility modulation therapy does not cause inappropriate inhibition of antibradycardic pacing which cannot be resolved by reprogramming or lead repositioning.

APPENDIX IV

Extrapolated Battery Life of the OPTIMIZER SMART IPG

The expected life of the Optimizer Smart IPG is limited by the expected service life of its rechargeable battery. The rechargeable battery inside the Optimizer Smart IPG should provide at least fifteen years of service. Over time and with repeated charging, the battery in the Optimizer Smart IPG will lose its ability to recover its full capacity.

Once the implant reaches its fifteenth year of service, it will have entered its elective replacement period. The Optimizer Smart IPG will need replacement when stimulation can no longer be maintained for a full week with routine weekly charging. In the fifteenth year of service, it is thus important that the patient will be instructed to fully charge the Optimizer Smart IPG seven days prior to routine checkup visits so that the physician may determine if the Optimizer Smart IPG is still able to deliver a full week of cardiac contractility modulation therapy when recharged weekly.

Replacement of the Optimizer Smart IPG is indicated once it can no longer maintain the delivery of CCM therapy for a full week with routine weekly charging

Extrapolated Battery Charge Longevity

The FDA approved dosage is 5 hours/day at 7.5V stimulation amplitude. Battery charge longevity can be estimated from the following tables. This is a conservative estimate of charge longevity for OPTIMIZER Smart IPG at 5 and 7.5V.

For CCM™ delivery of 7 hours per day as a function of parallel lead impedance:

Channels impedance (OHM)	Stimulation amplitude (V)	Charge longevity (days)
220	5	20
220	7.5	11
300	5	26
300	7.5	15
600	5	46
600	7.5	28
900	5	60
900	7.5	38
1200	5	65
1200	7.5	44

This is the same but at 5 hours per day. The FDA approved dosage is 5 hours per day.

Channels impedance (OHM)	Stimulation amplitude (V)	Charge longevity (days)
220	5	28
220	7.5	13

Channels impedance (OHM)	Stimulation amplitude (V)	Charge longevity (days)
300	5	36
300	7.5	18
600	5	65
600	7.5	34
900	5	84
900	7.5	46
1200	5	90
1200	7.5	54

These are for the following conditions:

- Number of pulses per CCM™ train: 2
- Phase duration: 5.14 ms
- Heart rate: 85 bpm

Under these conditions, the average current drain from the battery during CCM™ delivery is approximately as follows:

VBAT (V)	Impedance (OHM)	Stimulation amplitude (V)	Average Measured Current Drain (µA)
3.4	220	5	1,420
3.4	220	7.5	2,603
3.4	300	5	1,094
3.4	300	7.5	1,848
3.4	600	5	613
3.4	600	7.5	1,015
3.4	900	5	468
3.4	900	7.5	734
3.4	1200	5	412
3.4	1200	7.5	596
4.1	220	5	1,159
4.1	220	7.5	2,124
4.1	300	5	909
4.1	300	7.5	1,652
4.1	600	5	511
4.1	600	7.5	879
4.1	900	5	402
4.1	900	7.5	652
4.1	1200	5	394
4.1	1200	7.5	582

Failure to recharge the OPTIMIZER Smart IPG in a timely manner may cause the device to revert to Standby (OOO) mode and to suspend CCM™ signal delivery. In this mode, the device has to be recharged first before it resumes therapy delivery.

APPENDIX V

Scientific Background About Heart Failure and Cardiac Contractility Modulation

Heart failure is a condition wherein the heart muscle does not pump blood as well as it should, generally resulting in reduced cardiac output, possibly due to reduced contraction force or impaired relaxation or other deficiencies. Chronic heart failure is associated with cardiac muscle remodeling, which is the result of abnormal genomic, molecular, cellular, and structural changes that typically manifest clinically as changes in size, shape, and function of the heart's ventricles. The reduced cardiac function is associated with multiple symptoms, such as fatigue, shortness of breath (dyspnea), co-morbidities, and limited ability to walk, exercise or tolerate effort. The severity of symptoms is often classified by the physician in accordance with New York Heart Association (NYHA) classification (for example, NYHA class II represents moderate symptoms and class IV represents severe symptoms). Over time, chronic heart failure is a leading cause for hospitalizations and mortality. There are several medications that are used for treating heart failure according to the guidelines. In patients that are symptomatic despite appropriate medication, further evaluation of left ventricular ejection fraction (usually valuated by echocardiography) and QRS duration (evaluated by ECG) are useful in determining the possible need for an ICD, in cases having low ejection fraction, or a CRT, in cases with wide QRS, respectively.

Cardiac Contractility Modulation therapy is based on the delivery of non-excitatory electrical signals to the ventricles during the ventricular absolute refractory period. Published scientific research on cardiac contractility modulation therapy in animals and in humans explored various properties and effects. Some data suggests that cardiac contractility modulation has immediate effects on heart failure tissue, including potentially increasing the contraction force (contractility) of the muscle, possibly by immediate (i.e. less than a minute) improvement in the activity of the intracellular proteins that are associated with calcium cycling, for example by increased phosphorylation of the phospholamban protein, which is believed to modify the activity level of SERCA-2a, a protein responsible for intracellular calcium handling. Other data in heart failure animals and in humans suggest that after treating with cardiac contractility modulation for several hours, there may be normalization of mRNA expression levels of plurality of cardiac genes that are associated with heart failure (e.g. SERCA-2a, ANP, BNP, a-MHC, and others). Some data suggest that these changes and improvements in contraction are not associated with increase in myocardial oxygen consumption. Other data in animals over a period of a few months of cardiac contractility modulation delivery suggest the potential for improvements in the expression levels of several proteins that are associated with heart failure. In addition, some data suggest that with a few months of cardiac contractility modulation delivery, cardiac dimensions, structure, function (e.g. LVEDD, LVESD, and LVEF), cellular function, and/or tissue behavior may improve, providing the

potential for reverse remodeling. Other studies explored clinical benefits with cardiac contractility modulation therapy in chronic heart failure patients, typically with a narrow QRS and New York Heart Association (NYHA) class of at least II, and suggest that several months (e.g. at least 3 months) of treatment potentially result in improvements in exercise tolerance (e.g. by six minute walk tests or by peak oxygen consumption in cardio pulmonary tests) and in quality of life (e.g. by NYHA classification or by questionnaire), which could be indicative of clinically significant improvements in cardiac function. Various studies explored effects of cardiac contractility modulation in patients with NYHA classes II, III, and IV, some with EF up to 35%, some with higher EF (e.g. 40%, 45%). The studies usually included population with a range of age, gender, etiology (e.g. ischemic, idiopathic) and other characteristics.

With regard to use of cardiac contractility modulation outside the United States, the 2016 European Society of Cardiology practice guidelines has reviewed clinical studies of cardiac contractility modulation in heart failure patients and mentioned cardiac contractility modulation as a treatment option that may be considered in selected patient population. Summaries of some of these studies are available on Impulse Dynamics' website (http://www.impulse-dynamics.com/int/for-physicians/clinical-data/).

Over the years of evaluation of cardiac contractility modulation therapy and use of the therapy outside the USA in countries that accept the CE Mark, CCM™ was delivered using various models of the OPTIMIZER® System, which includes an implantable pulse generator (IPG) that is programmable and has a rechargeable battery. In principle, the OPTIMIZER® System is implanted in a procedure which is similar to a pacemaker implantation. Unlike pacemakers or defibrillators, the OPTIMIZER® System does not have integrated pacing or defibrillation capabilities, and is only used for delivering cardiac contractility modulation therapy. Often a patient may have concomitant implantable devices, as may be indicated per patient. The OPTIMIZER® is connected to the heart's ventricles using leads, typically with the electrodes fixated to the right ventricular septum. For example, the ventricular leads may be spaced apart by a few centimeters and positioned on the septum, at or adjacent to an intersection of the septum and right ventricular free wall. The electrodes are used for sensing electrical activity of the heart and for delivery of CCM™ signals to the ventricular muscle at the proper timing and signal configuration. The OPTIMIZER can be programmed to deliver cardiac contractility modulation therapy for several hours every day: typically 5 hours per day in the US studies, and 7 or more hours per day in other countries. As part of the OPTIMIZER algorithm, the circuitry records one or more local electrical activity (i.e. activity in the vicinity of the electrode measured using the bipolar electrode configuration) or non-local electrical activity (i.e. wide-field electrogram using unipolar sensing between the electrode and the distant IPG can). The timing of the CCM™ delivery is determined to be at a certain delay and duration from the sensing, designed to deliver the CCM™ during the absolute refractory period of the muscle within the current beat cycle; this may maintain the CCM™ signal non-excitatory. If the patient has a concomitant pacing or defibrillation device, the OPTIMIZER can be configured to apply the CCM™ signals during a paced cardiac cycle, within the refractory period

which follows the pacing. The OPTIMIZER can also be configured to apply the CCM™ signal during a non-paced cardiac cycle. The algorithm also applies criteria for delivery of the CCM™ signal or inhibiting the delivery of the CCM™ signal according to the relative timing of events, for example using criteria for minimum and maximum acceptable heart rate (R-R intervals), minimum and maximum acceptable time between sensed events in two locations on the RV septum, inhibition if signals are detected at an unexpected timing, and/or the use of an alert window in order to detect unexpected events and potentially block CCM™ delivery. Thus, the OPTIMIZER may deliver the non-excitatory CCM™ signal during the absolute refractory period of hundreds or thousands of beats out of 50,000 consecutive beats, taking into account the detection of any conditions that inhibit the CCM™ signal delivery (such as, for example, a detected arrhythmia). The parameters of the algorithm are configured per patient, with the purpose of enabling the normal delivery of the contractility modulating signal when the trace of events is indicative of an expected activation sequence of the heart.

APPENDIX VI

A. Current Clinical Summary: FIX-HF-5C

1.0 Study Design

FIX-HF-5C was a prospective, randomized, third-party blinded, multicenter study involving 160 patients. Key inclusion criteria included EF ≥ 25% and ≤ 45%, normal sinus rhythm, QRS duration <130 ms and NYHA Class III or ambulatory IV heart failure despite GDMT (including ICD when indicated). Main exclusion criteria included baseline peak VO_2 < 9 or > 20 mL/min/kg, hospitalization for heart failure 30 days before enrollment, clinically significant ambient ectopy (> 8,900 premature ventricular contractions [PVCs] / 24 hours), PR interval
> 375 ms, and chronic atrial fibrillation or atrial flutter within 30 days of enrollment.

A device implant date was scheduled for all eligible patients, which served as the study start date (SSD) for all patients. Patients were then randomized 1:1 to either continued OMT alone (control group) or OMT plus CCM (CCM group). Patients randomized to the CCM group were implanted with the device and the implant date was canceled for patients randomized to the control group. Patients returned to the clinic for evaluation at 2 weeks, 12 weeks, and 24 weeks. Follow-up visits included 2 CPX tests, a blinded NYHA assessment, MLWHFQ quality of life assessment, and an assessment of adverse events (AEs).

Blinding of NYHA and CPX

NYHA was assessed by a blinded on-site clinician according to their standard clinical practice.

CPX tests were assessed by an independent core laboratory blinded to the randomization assignment of individual patients.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was defined as the change in peak VO_2 from baseline at 24-weeks between the control and CCM groups as evaluated by the blinded core laboratory. The primary effectiveness analysis employed a Bayesian repeated measures linear model to estimate group differences in mean peak VO_2 at 24 weeks from baseline, with fixed 30% borrowing of information (70% down-weighting) from the corresponding treatment group difference observed in the FIX-HF-5 study subgroup defined as EF ≥ 25%.

Secondary Effectiveness Endpoints

Because there were multiple secondary hypotheses being tested, the method of alpha control was the closed form hierarchical method. For these analyses, if the one-sided p-value for the secondary endpoint was ≤ 0.025, the null hypothesis was rejected, and the next secondary endpoint was tested. The hierarchy for testing the secondary endpoints is the following:

- Minnesota Living with Heart Failure Questionnaire
- NYHA classification
- Peak VO_2 with a peak respiratory equivalent ratio (RER) ≥ 1.05

Safety Endpoints

The primary safety endpoint was the proportion of patients experiencing an OPTIMIZER device- or procedure-related complication through the 24-week follow up period as determined by the events adjudication committee (EAC). The primary safety endpoint was evaluated against a prespecified performance goal of 70% which was derived from several prior studies involving CRT (PMAs P010012: Contak CD CRT D, P030005: Contak Renewal TR, P030035: St. Jude Frontier, and P010012/S37: Contak Renewal 3AVT; Van Rees, 2011).

Other safety endpoints included all-cause death, cardiovascular death, composite rate of all-cause death or all-cause hospitalizations, composite rate of cardiovascular death or worsening heart failure-related hospitalizations, and overall rate of AEs and SAEs.

2.0 Demographics and Baseline Characteristics

Of the 160 eligible patients, 74 were randomized to the CCM group and 86 were randomized to the control group. In the CCM group, 6 patients did not receive the device and 2 patients died prior to the 24-week visit (including 1 patient who died prior to randomization). In the control group, 4 patients died, and 3 patients withdrew prior to the 24-week visit.

The groups were well-balanced with regards to demographic and baseline characteristics (**Table** 1). Overall, the mean age was approximately 63 years. The majority of patients were white and male, and the etiology was predominantly ischemic cardiomyopathy, characteristics which are typical of recent heart failure studies. Average peak VO_2 at baseline was approximately 15 mL/kg/min, which is moderately reduced compared to the

normal population. Characteristics of the prospectively enrolled FIX-HF-5C patients were similar to those of the FIX-HF-5 subgroup used for Bayesian analysis (Table 1).

Table 1: Demographic and Baseline Characteristics

	FIX-HF-5C		FIX-HF-5 Subgroup (25% ≤ EF ≤ 35%)	
	CCM (N=74)	**Control (N=86)**	**CCM (N=117)**	**Control (N=112)**
Mean Age (years)	63	63	59	60
Male	73%	79%	71%	74%
White	74%	71%	75%	72%
Ischemic Heart Failure	62%	59%	72%	69%
Prior MI	49%	59%	67%	59%
Prior PM/ICD System	88%	85%	80%	79%
Diabetes	51%	49%	49%	52%
NYHA				
Class III	87%	91%	93%	87%
Class IV	14%	9%	7%	13%
QRS Duration (ms)	103	104	99	101
LVEF (%)	33	33	31	32
LVEDD (mm)	58	60	57	56
Peak VO_2 (mL/kg/min)	15.5	15.4	14.6	14.8
Exercise Time (minutes)	11.4	10.6	11.3	11.7
6MHW (meters)	317	324	326	324
MLWHFQ (total score)	56	57	60	56

Mean or % (n/N)

3.0 Effectiveness Results

a. Primary Effectiveness Endpoint

The primary effectiveness endpoint was met. The model-based estimated mean difference in peak VO_2 at 24 weeks between CCM and control groups was 0.84 mL/kg/min with a 95% Bayesian credible interval of (0.12, 1.55) mL/kg/min. The probability that CCM is superior to control was 0.989, which exceeds the 0.975 criterion required for statistical significance of the primary endpoint.

Figure 1 shows that the Bayesian model's point estimate is very similar to the estimate from just the FIX-HF-5C study. However, the model further incorporates the high quality data from the previous randomized, blinded trial which increases the precision of the estimate. If FIX-HF-5C were a standalone trial, the middle CI would be appropriate. However, the Bayesian model allows us to incorporate the totality of the clinical experience which is an increased precision in the effect size estimate and is shown by the narrower 95% CI with the Bayesian estimate.

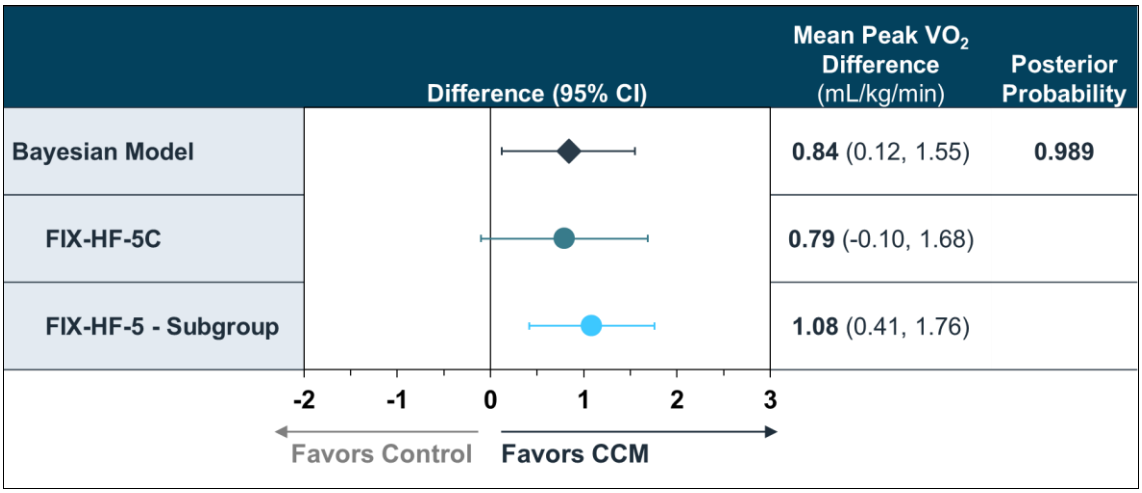


Figure 1: Peak VO_2 by Study

The improvement in peak VO_2 built up over time, from 3 to 6 months (Figure 2). The treatment effect can be seen in this graph to be a result of a significant decrease in VO2 for the control group with relatively little increase in VO2 for the treatment group.

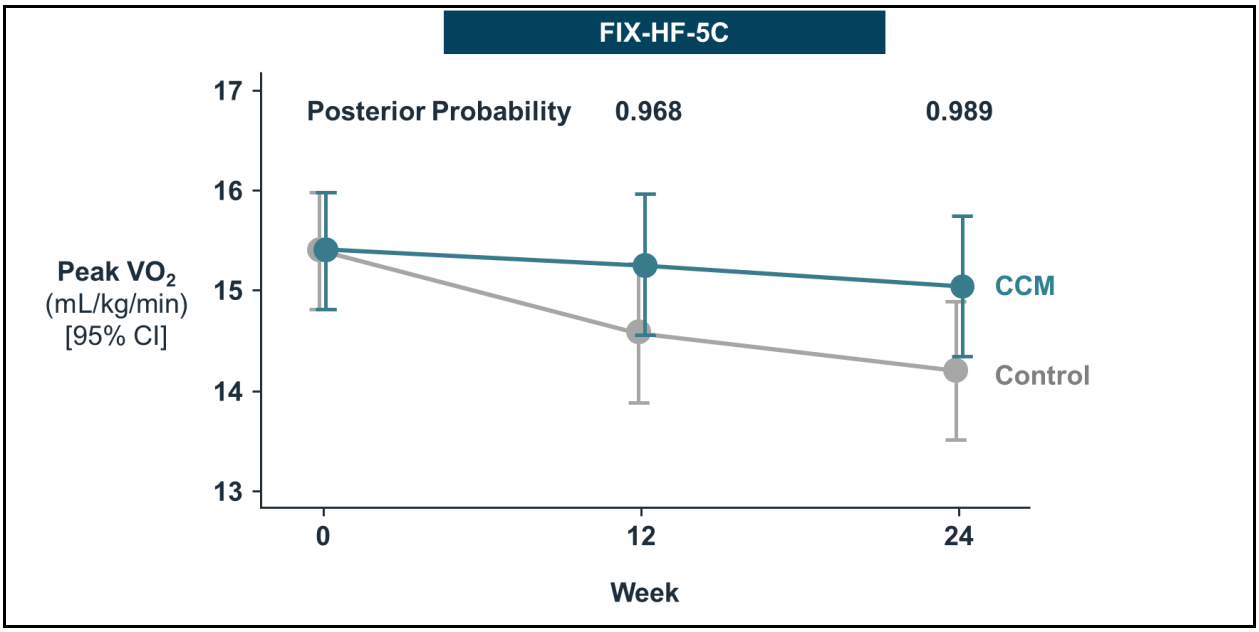


Figure 2: Time Course of Treatment Effect on Peak VO_2 (FIX-HF-5C)

Sensitivity analyses involving the primary effectiveness endpoint were conducted in which missing data were handled with different mechanisms or modifications (**Table**2). Method of imputation affected the results and the VO2 estimate varied from 0.48 to 0.84 depending on method. The conclusion of CCM superiority with respect to mean peak VO_2 was consistent across all sensitivity analyses. In addition, the primary analysis would achieve statistical significance with any borrowing weight of 0.11 or larger (as noted above, 0.30 was pre-specified in the analysis plan).

Table 2: Peak VO_2 Treatment Effect Across Studies

Study	Population	Bayesian VO_2 Estimate	Bayesian Posterior Probability
Primary Analysis with Borrowing FIX-HF-5C & FIX-HF-5	Imputation (Death = 0)	0.836	0.989
	Imputation (Death = lowest peak VO_2)	0.693	0.988
	Completed Cases (No Imputation)	0.603	0.978
Pooled FIX-HF-5C & FIX-HF-5	Completed Cases (No Imputation)	0.749	0.999
FIX-HF-5C Alone	Imputation (Death = 0)	0.799	0.960
	Imputation (Death = lowest peak VO_2)	0.611	0.957
	Completed Cases (No Imputation)	0.480	0.916
FIX-HF-5 Alone	Imputation (Death = 0)	1.074	1.00
	Completed Case (No Imputation)	1.080	1.00

b. Secondary Effectiveness Endpoints

MLWHFQ results at 24 weeks are presented in Table 3 and show that the CCM group was statistically significantly superior over the control group ($p < 0.001$) in each study.

Table 3: Change in MLWHFQ at 24 Weeks by Study

	Difference (95% CI) in MLWHFQ Total Score Between Groups	p-value (1-sided)
Pooled data	-10.9 (-14.6, -7.2)	< 0.001
FIX-HF-5C	-11.7 (-17.6, -5.9)	< 0.001
FIX-HF-5 Subgroup	-10.8 (-15.6, -6.1)	< 0.001

The percentage of patients improving by 1 or more NYHA class by study was statistically significantly superior in the CCM group compared to the control group ($p < 0.001$ in each study; Table 4).

Table 4: Patients Achieving ≥ 1 Class Improvement in NYHA at 24 Weeks by Study

Change in ≥ 1 Class in NYHA Class	CCM	Control	p-value (1-sided)
Pooled data	104/173 (60.1%)	59/169 (34.9%)	< 0.001
FIX-HF-5C	57/70 (81.4%)	32/75 (42.7%)	< 0.001
FIX-HF-5 Subgroup	47/103 (45.6%)	27/94 (28.7%)	< 0.001

In the FIX-HF-5C study, the p-value for the comparison of mean peak VO_2 at 24 weeks for CCM compared to control among observations with RER > 1.05 was 0.1100. Therefore, this secondary effectiveness endpoint was not met with FIX-HF-5C data

alone. When data were pooled from the FIX-HF-5 and FIX-HF-5C studies, the treatment effect was estimated as 0.62 mL/kg/min with a p-value of 0.009. In addition, the endpoint was met in the FIX-HF-5 subgroup (Table 5).

Table 5: Change in Peak VO_2 in Tests with RER ≥ 1.05 at 24 Weeks by Study

	Difference (95% CI) in Peak VO_2 (mL/kg/min) Between Groups	**p-value (1-sided)**
Pooled data	0.62 (0.11. 1.14)	0.009
FIX-HF-5C	0.43 (-0.25, 1.11)	0.1100
FIX-HF-5 - Subgroup	0.83 (0.06, 1.61)	0.017

A significant treatment effect was observed in 6 exploratory outcomes. There was no significant effect on change in VE/VCO_2 at 24 weeks.

4.0 Safety Results

The incidence of AEs in this study was relatively low. Comparisons between the groups did not show any statistical differences between CCM and control groups with respect to any AE tabulated for the analysis.

a. Primary Safety Endpoint

The primary safety endpoint was met as shown in **Table** 6. The complication-free proportion in the CCM group cohort was 89.7% (61/68) with lower confidence limit of 79.9% (one-sided alpha=0.025), which was greater than the pre-defined threshold of 70%. The majority of complications (5/7, 71.4%) were lead dislodgements.

Table 6: Primary Safety Endpoint (FIX-HF-5C, As Treated CCM Group Only)

Complication Free Rate n/N (%)	**95% LCL**	**95% UCL**
61/68 (89.7%)	79.9%	95.8%

b. Secondary Safety Endpoints (FIX-HF-5C)

As shown in Table 7, the freedom from death, freedom from cardiovascular death, and freedom from all-cause death or all-cause hospitalization at 24 weeks were similar in both groups.

Table 7. Secondary Safety Endpoints at 24 Weeks (FIX-HF-5C)

Freedom from	**CCM**	**Control**	**p-value**
All-cause death	98.3%	95.3%	0.2549
Cardiovascular death	100%	96.5%	0.1198
All-cause death or all-cause hospitalization	78.1%	77.7%	0.9437

B. Current Clinical Summary: FIX-HF-5C2

Introduction

Prior versions of the OPTIMIZER device used under the current US IDE have required sensing of atrial depolarization via an atrial lead to properly time the delivery of CCM pulses. Accordingly, the presence of atrial fibrillation or flutter imposed a technical limitation to the delivery of CCM signals. The current version of the OPTIMIZER, the 2-Lead OPTIMIZER Smart, has overcome the need for atrial sensing while maintaining safe and effective delivery of CCM to the ventricle. The 2-Lead OPTIMIZER Smart reduces the total lead requirement from 3-leads to 2-leads enabling CCM therapy to be delivered to a broader range of symptomatic HF patients while reducing the total hardware burden and corresponding lead-related adverse events on all patients receiving CCM.

The most frequent complications observed in the FIX-HF-5 and FIX-HF-5C trials were lead dislodgment, lead insulation breech and lead fracture requiring an additional surgery to revise or replace the lead. Similarly, such lead-related complications are the most frequently cited complications for CRT, ICD and pacemaker devices. Therefore, the ability to reduce the total number of leads needed for any given device, such as the OPTIMIZER Smart, has the potential to reduce the overall complication rate of that device. Improving the inherent safety of the OPTIMIZER Smart will allow physicians to expand its use thereby helping more patients with chronic heart failure.

1.0 Overview of Study Design

The FIX-HF-5C2 study was a multicenter, prospective, single-arm treatment only study of the 2-Lead configuration of the OPTIMIZER Smart System. Sixty patients were enrolled and implanted with the OPTIMIZER Smart System. The primary effectiveness endpoint was an improvement in exercise tolerance as measured by peak VO2 obtained on cardiopulmonary exercise testing (CPX). CPX data were evaluated by an independent core laboratory. Results for subjects implanted with the OPTIMIZER Smart were compared to the peak VO2 results for the subjects in the control group of the FIX-HF-5C study with respect to mean change in peak VO2 at 24-weeks from baseline.

The secondary effectiveness endpoint for the FIX-HF-5C2 study was an assessment of the average daily amount of CCM therapy provided over the 24-week study. A comparison between the OPTIMIZER 2-lead device subjects in the FIX-HF-5C2 study was made to the OPTIMIZER 3-lead device subjects of the FIX-HF-5C study to determine whether or not there was a difference between the therapy provided by the two device configurations.

The primary safety endpoint in the FIX-HF-5C2 study was the percentage of subjects experiencing an OPTIMIZER device or procedure related complication through the 24-week follow up period. Complications were adjudicated by an independent events committee.

2.0 Overview of Methodology

Sites identified potential patients from their clinic's chronic heart failure population. The target patient population consisted of subjects with ejection fractions from 25 to 45% (inclusive) whose symptoms were consistent with NYHA functional class III or ambulatory NYHA Class IV. Informed consent was obtained from potential subjects who were then enrolled in the study to undergo baseline screening testing to determine eligibility for the study. Baseline screening exams included: a medical history, physical examination, medication history, blood testing, cardiopulmonary exercise testing (CPX) to determine peak VO2, echocardiography to determine left ventricular ejection fraction (LVEF), 12-Lead ECG, and an NYHA Class assessment. The CPX and echocardiography tests were evaluated by an independent core laboratory.

Subjects that passed baseline testing and eligibility criteria were scheduled to have the OPTIMIZER Smart with 2-leads implanted as soon as possible. Subjects then returned to the clinic for evaluation at 2 weeks, 12 weeks and 24 weeks following the initial implantation. At the 12-week and 24-week visits, subjects completed a physical examination, medication evaluation, blood testing, CPX test, NYHA assessment, and an assessment of adverse events. Data collection for assessment of the study endpoints was concluded with the 24-week visit.

3.0 Results

3.1 Number of Investigators and Number of Sites

There were 8 sites participating in the FIX-HF-5C2 study and 8 principal investigators are shown in *Table 1 b*elow.

Table 1: List of Sites

Investigator/Investigational Site	Screened	Enrolled
Site A	7	4 (6.7%)
Site B	33	18 (30.0%)
Site C	3	1 (1.7%)
Site D	43	12 (20.0%)
Site E	8	3 (5.0%)
Site F	14	3 (5.0%)
Site G	6	1 (1.7%)
Site H	39	18 (30.0%)
TOTAL	**153**	**60**

3.2 Accountability of Subjects with Study Visits

Table 2 contains patient disposition. There were 153 subjects screened. Of these 60 subjects were enrolled and all 60 subjects were implanted with the study device. One subject withdrew prior to 24 weeks. There were no deaths. Follow-

up by study visit is presented in the table along with the number and percent of subjects who successfully completed exercise testing for the primary endpoint. A total of 53 subjects returned for exercise testing at 12 weeks while 55 subjects completed the exercise testing visit at 24 weeks. One (1) subject had his testing deemed inadequate at 12 weeks while 3 subjects had inadequate tests at 24 weeks, leaving 52 evaluable tests at 12 weeks and 52 evaluable tests at 24 weeks. One subject withdrew from the study prior to 24 weeks.

Table 2: Patient Disposition.

Variable	FIX-HF-5C2 OPTIMIZER
Screened	153
Enrolled / Implanted	60 (39.2%)
Per Protocol (PP)	59 (98.3%)
Died[1]	0 (0.0%)
Withdrawn[1]	1 (1.7%)
12 Week Visit Completed	59 (98.3%)
12 Week Exercise Tolerance Test Completed	53 (88.3%)
12 Week Exercise Tolerance Test Evaluable[2]	52 (86.7%)
24 Week Visit Completed	59 (98.3%)
24 Week Exercise Tolerance Test Completed	55 (91.7%)
24 Week Exercise Tolerance Test Evaluable[2]	52 (86.7%)

[1] Prior to 24 Week Visit
[2] Includes only subjects with valid Peak VO_2, as determined by the core lab, at the indicated visit.

3.3 Baseline Characteristics

Baseline characteristics of subjects in the FIX-HF-5C2 study are presented in ***Table 4*** along with baseline characteristics of the FIX-HF-5C study groups. Of primary note are the comparisons between the OPTIMIZER group in the FIX-HF-5C2 study and the Control group from the FIX-HF-5C study, as these groups form the primary comparison groups for the efficacy analyses. At a nominal 0.05 level of significance, FIX-HF-5C2 subjects were older (66.3 ± 8.9 vs 62.8 ± 11.4), had a lower prevalence of diabetes (30% vs. 48.8%), and a lower LVEDD value (57.7 ± 6.8 vs. 60.2 ± 7.0) than subjects in the FIX-HF-5C Control group. Although FIX-HF-5C2 subjects had a smaller LVEDD, LVEF between the two groups (34.1 + 6.1 vs. 32.5 + 5.2%) was not statistically significantly different. Peak VO2 on CPX testing at baseline was similar between the two groups, but the FIX-HF-5C2 subjects exercised for a full minute longer on average than the FIX-HF-5C control group subjects (11.6 + 2.9 vs. 10.6 + 3.1 minutes). This difference was statistically significant ($p<0.04$).

Consistent with the study purpose and design, significantly more subjects in the FIX-HF-5C2 study had permanent atrial fibrillation at baseline as evidenced by the presence of atrial fibrillation on the baseline ECG tracing. Although it did not reach statistical significance, there was only 1 NYHA Class IV subject in FIX-HF-5C2 while 8 subjects were NYHA Class IV in FIX-HF-5C. This difference reflects clinical practice. It is not a regulatory limitation as the protocol was established before the Indications for Use were narrowed to NYHA III subjects and NYHA IV subjects were allowed in the FIX-HF-5C2 study. The clear clinical practice selection of NYHA Class III subjects in the FIX-HF-5C2 study confirms that the NYHA III functional class group is the appropriate target for CCM therapy. All other characteristics were similar between the two groups.

Baseline medication usage is presented in the ***Table 5.***

Table 4: Baseline Characteristics: ITT Population

	FIX-HF-5C2	FIX-HF-5C			
Variable	**OPTIMIZER**	**OPTIMIZER**	**P-value[1]**	**Control**	**P-value[1]**
Age (yrs)	66.3 ± 8.9 (60)	63.1 ± 10.9 (74)	0.071	62.8 ± 11.4 (86)	0.049
Male	53 (88.3%)	54 (73.0%)	0.032	68 (79.1%)	0.182
Ethnicity (White)	40 (66.7%)	55 (74.3%)	0.346	61 (70.9%)	0.590
CHF Etiology (Ischemic)	41 (68.3%)	46 (62.2%)	0.473	51 (59.3%)	0.299
Prior MI	36 (60.0%)	36 (48.6%)	0.224	51 (59.3%)	1.000
Prior CABG	13 (21.7%)	18 (24.3%)	0.837	23 (26.7%)	0.560
Prior ICD or PM System	55 (91.7%)	67 (94.4%)	0.731	73 (85.9%)	0.432
Prior ICD (ICD,CRT-D,S-ICD)	53 (88.3%)	66 (93.0%)	0.382	73 (85.9%)	0.804
Prior PM	2 (3.3%)	1 (1.4%)	0.593	0 (0.0%)	0.170
Angina	2 (3.3%)	5 (6.8%)	0.459	6 (7.0%)	0.471
Diabetes	18 (30.0%)	38 (51.4%)	0.014	42 (48.8%)	0.027
Baseline Permanent Atrial Fibrillation	9 (15.0%)	0 (0%)	0.0005	0 (0%)	0.0002
History of Atrial Arrhythmias	34 (56.7%)	25 (33.8%)	0.009	35 (40.7%)	0.065
Atrial Flutter	5 (8.3%)	8 (10.8%)	0.772	6 (7.0%)	0.761
Atrial Fibrillation	28 (46.7%)	20 (27.0%)	0.029	27 (31.4%)	0.082
Frequent PACs	3 (5.0%)	3 (4.1%)	1.000	1 (1.2%)	0.306
Other Atrial Abnormalities	2 (3.3%)	2 (2.7%)	1.000	3 (3.5%)	1.000
History of Ventricular Arrhythmias	17 (28.3%)	26 (35.1%)	0.459	28 (32.6%)	0.716
Ventricle Fibrillation	5 (8.3%)	5 (6.8%)	0.752	8 (9.3%)	1.000
Ventricular Tachycardia	13 (21.7%)	19 (25.7%)	0.685	19 (22.1%)	1.000
Frequent PVCs	5 (8.3%)	8 (10.8%)	0.772	7 (8.1%)	1.000
NYHA					
Class III	59 (98.3%)	64 (86.5%)	0.023	78 (90.7%)	0.082
Class IV	1 (1.7%)	10 (13.5%)	0.023	8 (9.3%)	0.082

[1]Compared to FIX-HF-5C2 OPTIMIZER Group via Fishers exact test for binary variables and two-sample t-test for continuous variables.

Table 5: Baseline Medications: ITT Population

	FIX-HF-5C2	FIX-HF-5C			
Variable	**OPTIMIZER**	**OPTIMIZER**	**P-value[1]**	**Control**	**P-value[1]**
ACEi/ARB/ARNi	45 (75.0%)	61 (82.4%)	0.393	72 (83.7%)	0.212
ACE inhibitor	29 (48.3%)	40 (54.1%)	0.603	49 (57.0%)	0.317
ARB	8 (13.3%)	18 (24.3%)	0.128	22 (25.6%)	0.096
ARNi	9 (15.0%)	3 (4.1%)	0.035	3 (3.5%)	0.028
Beta Blocker	57 (95.0%)	72 (97.3%)	0.656	82 (95.3%)	1.000
Diuretic	44 (73.3%)	57 (77.0%)	0.689	67 (77.9%)	0.558
Secondary Diuretic	5 (8.3%)	6 (8.1%)	1.000	8 (9.3%)	1.000
Ivabradine	3 (5.0%)	2 (2.7%)	0.656	4 (4.7%)	1.000
Digoxin	4 (6.7%)	10 (13.5%)	0.260	8 (9.3%)	0.762
Aldosterone Inhibitor	25 (41.7%)	26 (35.1%)	0.477	33 (38.4%)	0.733
Hydralazine	3 (5.0%)	5 (6.8%)	0.731	10 (11.6%)	0.240
Nitrates	11 (18.3%)	18 (24.3%)	0.527	26 (30.2%)	0.124
Calcium Channel Blocker	6 (10.0%)	9 (12.2%)	0.787	8 (9.3%)	1.000
Anti-arrhythmic	19 (31.7%)	14 (18.9%)	0.108	12 (14.0%)	0.013
Anti-platelet	41 (68.3%)	54 (73.0%)	0.572	59 (68.6%)	1.000
Anticoagulant	27 (45.0%)	19 (25.7%)	0.028	18 (20.9%)	0.003

[1]Compared to FIX-HF-5C2 OPTIMIZER Group via Fishers exact test.

Baseline heart failure medications are summarized in ***Table 5.*** The only significant differences were a greater use of ARNi's, anti-arrhythmics, and anticoagulants in FIX-HF-5C2 subjects. The greater ARNi use reflects the fact that they were introduced toward the end of the FIX-HF-5C study. The greater use of anti-arrhythmics and anticoagulants likely represents the inclusion of patients with atrial fibrillation; those patients were excluded in the FIX-HF-5C study. ***Table 6*** breaks down the anti-arrhythmic medication usage in FIX-HF-5C2 and FIX-HF-5C studies for comparison.

Table 6: Baseline Anti-arrhythmic Medications

	FIX-HF-5C2	**FIX-HF-5C**	
Variable	**OPTIMIZER**	**OPTIMIZER**	**Control**
Anti-arrhythmic	19 (31.7%)	14 (18.9%)	12 (14.0%)
Amiodarone	12 (20.0%)	11 (14.9%)	6 (7.0%)
Sotalol	5 (8.3%)	3 (4.1%)	2 (2.3%)
Mexiletine	1 (1.7%)	0	3 (3.5%)
Dofetilide	1 (1.7%)	0	1 (1.2%)

3.5 Primary Effectiveness Endpoint

a. Bayesian Analysis

A Bayesian repeated measures model was used to estimate group differences in the mean peak VO_2 at 24 weeks from baseline in FIX-HF-5C2 device patients compared to FIX-HF-5C control patients, with 30% borrowing of information (70% down-weighting) from the corresponding group difference observed in the FIX-HF-5 subgroup data.

In the FIX-HF-5C2 device group, 55 of the 60 patients provided at least one post-baseline peak VO_2 measurement, and 52 patients provided 24-week peak VO_2 measurements. There were no deaths in FIX-HF-5C2 subjects at the 24-week assessment period, and there were no missing observations due to heart failure hospitalizations. However, patients in the FIX-HF-5C control group who are missing peak VO_2 observations due to death are imputed as zeros per the FIX-HF-5C protocol. There are a total of 146 patients and 397 non-missing peak VO_2 observations in the combined FIX-HF-5C2 device and FIX-HF-5C control groups for this analysis.

Tables 7 and 8 provide results of the Bayesian analyses while Figures 1 and 2 show the peak VO2 results graphically.

Table 7: Number of Observations, Mean, SD of Peak VO2 by Group and Time

	Nobs(observed)		Nobs (missing)		Mean		Standard Deviation	
	Control	Device	Control	Device	Control	Device	Control	Device
Baseline	86	60	0	0	15.36	15.01	2.81	2.94
12 Weeks	73	52	13	8	14.59	16.01	4.29	3.34
24 Weeks	74	52	12	8	14.34	16.22	4.69	3.09

Table 8: Bayesian Primary Analysis Results (with Borrowing)

		Borrowing (Bayes)			
Time	TmtDiff	LL	UL	SE	P(Superior)
12 Weeks	1.079	0.381	1.776	0.356	0.999
24 Weeks	1.722	1.021	2.417	0.356	1.000

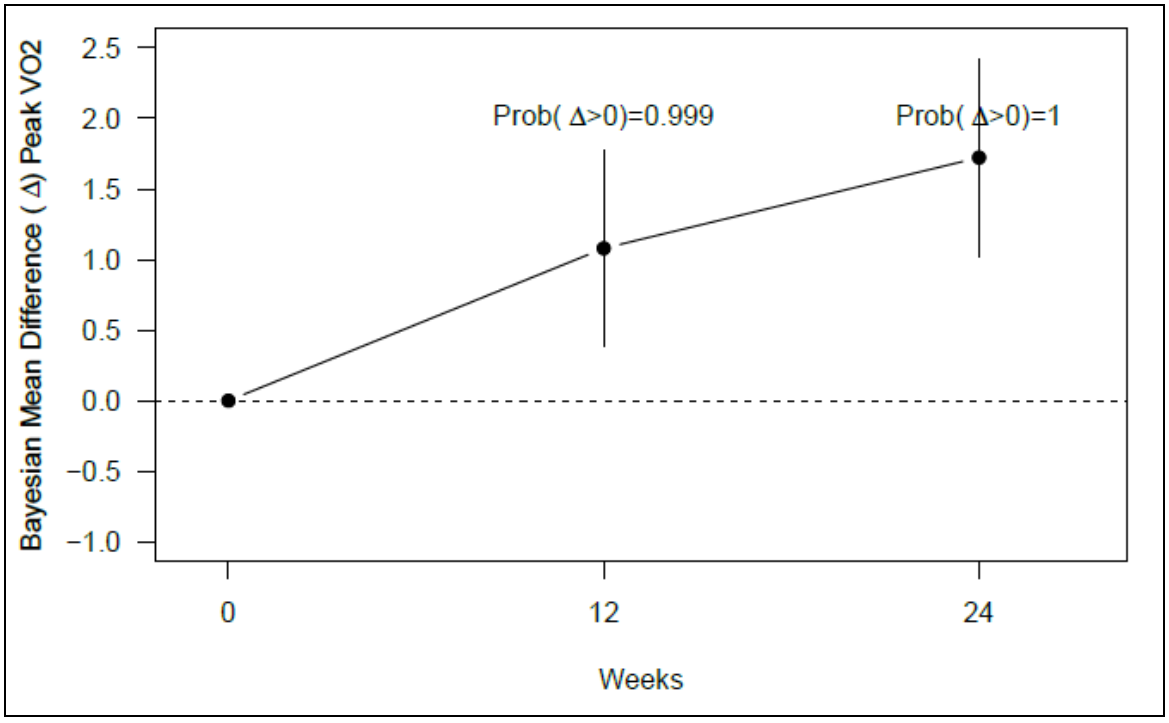


Figure 1:Bayesian Modeled Treatment Mean Difference (Δ) Peak VO2 by Time

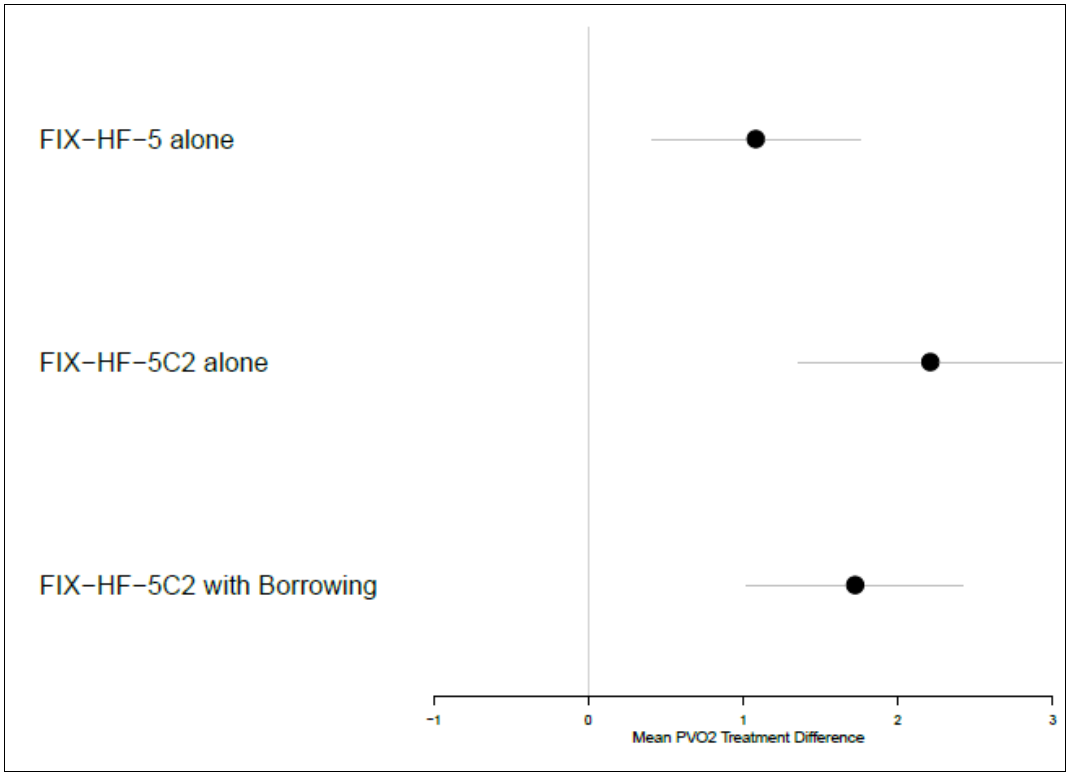


Figure2: 24-Week Modeled Mean PVO2 Treatment Difference by Study

The Bayesian Posterior Probability that Δ_3 is greater than 0 (indicating superiority of FIX-HF-5C2 device to FIX-HF-5C control) is 1. Because this exceeds 0.975, the null hypothesis is rejected and superiority is claimed with respect to the primary endpoint.

b. Frequentist Analysis

The Bayesian analysis indicates that the FIX-HF-5C2 OPTIMIZER group had a superior increase in Peak VO2 over the FIX-HF-5C Control group with a posterior probability which exceeds the 0.975 required for statistical significance.

A supporting, non-Bayesian analysis of Peak VO2 appears in ***Table 9***Error! Reference source not found. (overall summaries).

Eleven (11) subjects were missing evaluable Peak VO2 results at weeks 12 or 24. Five (5) subjects were missing at both visits.

There were no deaths or missingness due to heart failure hospitalizations so there were no imputations of zeros or lowest value in the FIX-HF-5C2 data. Previous study results are presented for comparative purposes including differences between the current OPTIMIZER results and results from the FIX-HF-5C study.

Peak VO2 was significantly increased at both 12 and 24 weeks in the FIX-HF-5C2 OPTIMIZER group and the change from baseline was significantly different from the control group in the FIX-HF-5C study. This was confirmed in the frequentist mixed model results compared to the FIX-HF-5C study control.

In total, we observed an improvement in peak VO_2 for the device subjects in the FIX-HF-5C2 study which was not dependent on a decrease in VO2 for the control group.

Table 9: Efficacy Summary: ITT Population

		FIX-HF-5C2	FIX-HF-5C			
Variable		**OPTIMIZER**	**OPTIMIZER**	**Difference[1]**	**Control**	**Difference[1]**
Peak VO2 (ml/kg/min)						
Baseline	Mean±SD (n)	15.0 ± 2.9 (60)	15.5 ± 2.6 (73)	-0.48 ± 2.76	15.4 ± 2.8 (86)	-0.36 ± 2.87
	(min,max)	(9.8, 19.9)	(9.8, 19.7)		(9.1, 19.9)	
	[95% CI]	[14.2,15.8]	[14.9,16.1]	[-1.44, 0.47]	[14.8,16.0]	[-1.31, 0.60]
	P-value[2]			0.317		0.462
12 Weeks	Mean±SD (n)	16.0 ± 3.3 (52)	15.6 ± 3.2 (67)	0.43 ± 3.25	15.2 ± 3.1 (70)	0.80 ± 3.20
	(min,max)	(10.2, 22.2)	(9.0, 23.3)		(8.5, 21.9)	
	[95% CI]	[15.1,16.9]	[14.8,16.4]	[-0.76, 1.62]	[14.5,15.9]	[-0.36, 1.96]
	P-value[2]			0.478		0.174
Change Baseline to 12 Weeks	Mean±SD (n)	0.77 ± 1.64 (52)	0.10 ± 2.34 (67)	0.67 ± 2.06	-0.35 ± 2.11 (70)	1.13 ± 1.92
	(min,max)	(-5.30, 4.60)	(-7.35, 5.95)		(-6.10, 4.80)	
	[95% CI]	[0.32,1.23]	[-0.47,0.67]	[-0.09, 1.42]	[-0.86,0.15]	[0.43, 1.82]
	P-value[2]	0.001	0.716	0.082	0.164	0.002
24 Weeks	Mean±SD (n)	16.2 ± 3.1 (52)	15.5 ± 3.5 (66)	0.73 ± 3.33	15.2 ± 3.3 (70)	1.06 ± 3.20
	(min,max)	(10.2, 23.9)	(8.9, 23.2)		(8.8, 22.7)	
	[95% CI]	[15.4,17.1]	[14.6,16.3]	[-0.49, 1.95]	[14.4,15.9]	[-0.10, 2.21]
	P-value[2]			0.239		0.074

		FIX-HF-5C2	FIX-HF-5C			
Variable		**OPTIMIZER**	**OPTIMIZER**	**Difference[1]**	**Control**	**Difference[1]**
Change Baseline to 24 Weeks	Mean±SD (n)	1.13 ± 1.50 (52)	-0.027 ± 2.745 (66)	1.15 ± 2.28	-0.50 ± 2.36 (70)	1.63 ± 2.04
	(min,max)	(-2.60, 4.20)	(-7.30, 5.90)		(-6.85, 4.90)	
	[95% CI]	[0.71,1.54]	[-0.701,0.648]	[0.32, 1.99]	[-1.07,0.06]	[0.89, 2.37]
	P-value[2]	<.001	0.938	0.007	0.078	<.001

[1]Compared to FIX-HF-5C2 OPTIMIZER Group.
[2]Values are compared to baseline using the paired t-test, and differences are compared using the two-sample t-test without taking into account other time points.

3.6 Secondary Effectiveness Analyses

Since the primary endpoint was met, the secondary endpoint of total CCM delivery could be formally tested. Total CCM delivery is presented in ***Table 10*** for the IP populations. Results are presented for all available data and for the multiple imputation approach as described previously. Although all subjects in FIX-HF-5C2 were implanted, 1 subject in the FIX-HF-5C OPTIMIZER group died prior to study start and an additional 5 subjects were not implanted, so the IP population differs for the FIX-HF-5C study used in comparison. As can be seen in ***Table 1*****,** for all available data and imputed data, the total CCM delivery at 24 weeks is equivalent between the OPTIMIZER groups of the FIX-HF-5C2 and FIX-HF-5C studies since the 95% confidence interval of the difference between the 2 groups lies wholly within the interval defined by (Θ_L,Θ_U).

Table 10: Secondary Efficacy - OPTIMIZER Interrogation: IP Population

		FIX-HF-5C2	FIX-HF-5C		FIX-HF-5C2 Bsl Permanent AFIB
Variable		**OPTIMIZER (N=60)**	**OPTIMIZER (N=60)**	**Difference[1]**	**OPTIMIZER (N=9)**
Total CCM Delivery					
24 Weeks	Mean±SD (n)	19892 ± 3472 (59)	19583 ± 4998 (67)	310 ± 4352	19734 ± 4187 (9)
	(min,max)	(11618, 28284)	(3645, 31009)		(12787, 24578)
	[95% CI]	[18988,20797]	[18364,20802]	[-1228, 1847]	[16515,22952]
	P-value[2]			0.691	
	(ThetaL,ThetaU)			(-2448,2448)	
Total CCM Delivery (IMPUTED)					
24 Weeks	Mean±SE	19897 ± 463	19618 ± 610	279 ± 783	
	(min,max)	(19811, 20037)	(19553, 19722)		
	[95% CI]	[18988,20805]	[18421,20814]	[-1256,1813]	
	P-value[2]			0.722	
	(ThetaL,ThetaU)			(-2452,2452)	

[1]Bioequivalence is conceded if the two-sided 95% confidence interval, for the difference, is completely contained within the interval (ThetaL,ThetaU).
[2]P-value for mean from the two-sample t-test for the difference between groups.

3.7 Primary Safety Endpoint

The primary safety endpoint was the composite endpoint of the percentage of subjects in the OPTIMIZER group who experienced either an OPTIMIZER device or OPTIMIZER procedure related complication through the 24-week follow-up period, as determined by an independent events adjudication committee (EAC). The EAC reviewed all serious adverse event reports (SAEs), confirmed the classification of "serious", and adjudicated the relationship of the event to the OPTIMIZER System device or procedure. SAEs that the EAC determined to be definitely related to either the OPTIMIZER System or the OPTIMIZER Procedure were considered a Complication.

There was only 1 complication observed in the FIX-HF-5C2 subjects. This was in a subject who had a minor hematoma at the OPTIMIZER IPG implant site and was kept in the hospital overnight for observation following the device implantation. The hematoma resolved without treatment, and there were no further complications in this case. The EAC adjudicated the event as a procedure related complication to account for the index hospital stay being prolonged an additional day for observation. There was no OPTIMIZER device-related SAE reported in the 2-lead device subjects.

Thus, the complication rate in FIX-HF-5C2 study ITT group was 1.7% (1/60) with exact 95% CI (0.0%, 8.9%). As can be seen in ***Table11***, the rate of complications in the FIX-HF-5C2 study was nominally lower than seen in the previous study although not statistically significant. The small sample size for the FIX-HF-5C2 study renders it difficult to show a statistical difference in percentage points. However, the absolute difference between the complication rate for the FIX-HF-5C2 study (1.7%) and the FIX-HF-5C study (10.3%) is clinically relevant.

We can therefore conclude that the primary safety endpoint of the FIX-HF-5C2 study was met and that delivery of CCM through a 2-Lead device is just as safe as delivery of CCM therapy through a 3-Lead device. These results may, in part, be due to a reduction in the number of leads implanted with the 2-Lead device as well as the reduction in the total volume of leads introduced in the venous vasculature.

Table 11: Safety: ITT Population

		FIX-HF-5C2	FIX-HF-5C	
Variable		**OPTIMIZER 2-lead**	**OPTIMIZER 3-lead**	**P-value[1]**
Primary Safety				
OPTIMIZER device- or procedure-related complication through 24 Weeks	n(%)	1 (1.7%)	7 (10.3%)	0.0660
	[95% CI]	(0.0%, 8.9%)	(4.2%, 20.1%)	
Secondary Safety				
PVC or VT SAEs	n(%)	0 (0.0%)	0 (0.0%)	
PVC	n(%)	0 (0.0%)	0 (0.0%)	
VT	n(%)	0 (0.0%)	0 (0.0%)	

[1]Compared to FIX-HF-5C2 OPTIMIZER Group via Fishers exact test.
* Values are number and percent of subjects. Subjects are counted only once within each category.

3.8 Adverse Events

All site reported non-serious adverse events and adjudicated serious adverse events from study start date to 24 weeks; are tabulated in ***Table 12*** and

Table in the ITT population. The total number of events and the number and percent of subjects having at least one event of the type listed is given. Event rates were similar to those seen in both the FIX-HF-5C OPTIMIZER and control groups. At a nominal 0.05 level of significance, there were fewer percentage of subjects that had a serious OPTIMIZER System malfunction in the FIX-HF-5C2 study than in the previous study (p=0.03).

Table 12: Adjudicated Serious Adverse Events, Day 0-168: ITT Population

	FIX-HF-5C2 OPTIMIZER		FIX-HF-5C OPTIMIZER			FIX-HF-5C Control		
Variable	**# Events**	**Subjects[2]**	**# Events**	**Subjects**	**P-value[1]**	**# Events**	**Subjects**	**P-value[1]**
All	26	19 (31.7%)	29	20 (27.0%)	0.572	27	19 (22.1%)	0.250
		(20.3%, 45.0%)		(17.4%, 38.6%)			(13.9%, 32.3%)	
General Medical	8	7 (11.7%)	7	7 (9.5%)	0.779	8	7 (8.1%)	0.571
		(4.8%, 22.6%)		(3.9%, 18.5%)			(3.3%, 16.1%)	
Arrhythmia	3	2 (3.3%)	3	3 (4.1%)	1.000	2	2 (2.3%)	1.000
		(0.4%, 11.5%)		(0.8%, 11.4%)			(0.3%, 8.1%)	
Worsening Heart Failure	7	5 (8.3%)	4	3 (4.1%)	0.466	8	7 (8.1%)	1.000
		(2.8%, 18.4%)		(0.8%, 11.4%)			(3.3%, 16.1%)	
General Cardiopulmonary	2	2 (3.3%)	4	3 (4.1%)	1.000	2	2 (2.3%)	1.000
		(0.4%, 11.5%)		(0.8%, 11.4%)			(0.3%, 8.1%)	
Bleeding	1	1 (1.7%)	0	0 (0.0%)	0.448	1	1 (1.2%)	1.000
		(0.0%, 8.9%)		(0.0%, 4.9%)			(0.0%, 6.3%)	
Neurologic	1	1 (1.7%)	0	0 (0.0%)	0.448	0	0 (0.0%)	0.411
		(0.0%, 8.9%)		(0.0%, 4.9%)			(0.0%, 4.2%)	
Thromboembolism	1	1 (1.7%)	1	1 (1.4%)	1.000	1	1 (1.2%)	1.000
		(0.0%, 8.9%)		(0.0%, 7.3%)			(0.0%, 6.3%)	
Local Infection	1	1 (1.7%)	1	1 (1.4%)	1.000	4	4 (4.7%)	0.649
		(0.0%, 8.9%)		(0.0%, 7.3%)			(1.3%, 11.5%)	
Sepsis	1	1 (1.7%)	1	1 (1.4%)	1.000	1	1 (1.2%)	1.000
		(0.0%, 8.9%)		(0.0%, 7.3%)			(0.0%, 6.3%)	
ICD or Pacemaker System Malfunction	1	1 (1.7%)	2	2 (2.7%)	1.000	0	0 (0.0%)	0.411
		(0.0%, 8.9%)		(0.3%, 9.4%)			(0.0%, 4.2%)	
OPTIMIZER System Malfunction	0	0 (0.0%)	6	6 (8.1%)	0.033		-	

	FIX-HF-5C2 OPTIMIZER		FIX-HF-5C OPTIMIZER			FIX-HF-5C Control		
Variable	**# Events**	**Subjects[2]**	**# Events**	**Subjects**	**P-value[1]**	**# Events**	**Subjects**	**P-value[1]**
		(0.0%, 6.0%)		(3.0%, 16.8%)				

Program Name: AE.sas

[1]Compared to FIX-HF-5C2 OPTIMIZER Group via Fishers exact test.

[2]Number and percent of subjects. Subjects are counted only once within each category.

Table 13: Non-Serious Adverse Events, Day 0-168: ITT Population

	FIX-HF-5C2 OPTIMIZER		FIX-HF-5C OPTIMIZER			FIX-HF-5C Control		
Variable	**# Events**	**Subjects[2]**	**# Events**	**Subjects**	**P-value[1]**	**# Events**	**Subjects**	**P-value[1]**
All	39	26 (43.3%)	41	21 (28.4%)	0.101	35	23 (26.7%)	0.050
		(30.6%, 56.8%)		(18.5%, 40.1%)			(17.8%, 37.4%)	
General Medical	23	19 (31.7%)	22	14 (18.9%)	0.108	23	13 (15.1%)	0.025
		(20.3%, 45.0%)		(10.7%, 29.7%)			(8.3%, 24.5%)	
Arrhythmia	1	1 (1.7%)	1	1 (1.4%)	1.000	4	4 (4.7%)	0.649
		(0.0%, 8.9%)		(0.0%, 7.3%)			(1.3%, 11.5%)	
Worsening Heart Failure	3	3 (5.0%)	6	5 (6.8%)	0.731	4	4 (4.7%)	1.000
		(1.0%, 13.9%)		(2.2%, 15.1%)			(1.3%, 11.5%)	
General Cardiopulmonary	4	4 (6.7%)	3	3 (4.1%)	0.700	3	3 (3.5%)	0.446
		(1.8%, 16.2%)		(0.8%, 11.4%)			(0.7%, 9.9%)	
Bleeding	2	2 (3.3%)	2	2 (2.7%)	1.000	0	0 (0.0%)	0.167
		(0.4%, 11.5%)		(0.3%, 9.4%)			(0.0%, 4.2%)	
Neurologic	0	0 (0.0%)	1	1 (1.4%)	1.000	0	0 (0.0%)	
		(0.0%, 6.0%)		(0.0%, 7.3%)			(0.0%, 4.2%)	
Thromboembolism	1	1 (1.7%)	0	0 (0.0%)	0.448	0	0 (0.0%)	0.411
		(0.0%, 8.9%)		(0.0%, 4.9%)			(0.0%, 4.2%)	
Local Infection	5	5 (8.3%)	3	3 (4.1%)	0.466	1	1 (1.2%)	0.043
		(2.8%, 18.4%)		(0.8%, 11.4%)			(0.0%, 6.3%)	
Sepsis	0	0 (0.0%)	0	0 (0.0%)		0	0 (0.0%)	
		(0.0%, 6.0%)		(0.0%, 4.9%)			(0.0%, 4.2%)	

	FIX-HF-5C2 OPTIMIZER		FIX-HF-5C OPTIMIZER			FIX-HF-5C Control		
Variable	**# Events**	**Subjects[2]**	**# Events**	**Subjects**	**P-value[1]**	**# Events**	**Subjects**	**P-value[1]**
ICD or Pacemaker System Malfunction	0	0 (0.0%)	0	0 (0.0%)		0	0 (0.0%)	
		(0.0%, 6.0%)		(0.0%, 4.9%)			(0.0%, 4.2%)	
OPTIMIZER System Malfunction	0	0 (0.0%)	3	2 (2.7%)	0.502		-	
		(0.0%, 6.0%)		(0.3%, 9.4%)				

Program Name: AE.sas

[1]Compared to FIX-HF-5C2 OPTIMIZER Group via Fishers exact test.

[2]Number and percent of subjects. Subjects are counted only once within each category.

The incidence of overall non-serious adverse events was significantly higher in the OPTIMIZER subject cohort of the FIX-HF-5C2 study than for the control group of the FIX-HF-5C study. It was not significantly greater than the incidence on non-serious adverse events in the OPTIMIZER group for the FIX-HF-5C study. The higher rate between the FIX-HF-5C2 OPTIMIZER subjects and subjects in the control group for FIX-HF-5C can be attributed to differences in general medical events and localized infection. General medical events include a wide range of adverse events such as sore throats to more serious events like cholelithiasis. Clinically, it is difficult to interpret the meaning of any differences in general medical events. Only 1 of the 5 non-serious localized infections was device related (IPG pocket). The important point is that the localized infection rate was not high to begin with and was not significantly different between the OPTIMIZER subjects for the FIX-HF-5C2 study and the OPTIMIZER subjects for the FIX-HF-5C study.

4.0 Discussion

The study met its primary effectiveness endpoint based on the Bayesian analysis presented which was supported by frequentist analyses. With respect to safety, there were no device-related complications and only 1 procedure-related complication (<2%). This was significantly lower than the rate observed in the FIX-HF-5C 3-lead device study. There was no evidence of a difference between study groups with respect to adverse events or adjudicated serious adverse events, although the FIX-HF-5C2 OPTIMIZER group appeared to have a lower rate of serious OPTIMIZER System related events than was seen previously.

Thus, it can be concluded that the FIX-HF-5C2 study met its pre-specified endpoints and that the 2-Lead configuration of the OPTIMIZER Smart is at least as safe and effective as the 3-Lead configuration of the OPTIMIZER Smart approved by FDA in P180036.

Peak VO2 improved more in the OPTIMIZER patients of the present FIX-HF-5C2 study than in the prior FIX-HF-5C study control group for both Bayesian and frequentist statistical analyses.

5.0 Risk-Benefit

The benefits of the 2-Lead configuration of the OPTIMIZER Smart are an improvement in peak VO2, improved functional status as evidenced by improvements in NYHA functional class and a reduced incidence of procedural complications as compared to the 3-Lead configuration of the OPTIMIZER Smart (FIX-HF-5C study). Risks associated with the OPTIMIZER Smart system are similar to those associated with ICDs and pacemakers; which are well documented in the literature. In the FIX-HF-5C2 study, lead dislodgments were the primary complication reported. There were no lead dislodgments reported in the FIX-HF-5C2 study. Thus, it is clear that the potential benefits of the 2-Lead configuration of the OPTIMIZER Smart outweigh the potential risks.

6.0 Conclusions

Based on the results of the FIX-HF-5C2 study described herein, we conclude the following:

1. The 2-Lead configuration of the OPTIMIZER Smart System is safe and effective for the delivery of CCM therapy in patients with NYHA class III heart failure symptoms.
2. Exercise tolerance as evidenced by improved peak VO2, is improved by CCM therapy delivered by the 2-Lead configuration of the OPTIMIZER Smart system.
3. CCM therapy delivery with the 2-Lead system is clinically effective and the same as delivery with the 3-Lead device.
4. Complication rates are lower with the 2-Lead device possibly due to the reduction in the number of implanted leads.
5. The serious adverse event profile for the 2-Lead device is not significantly different from that with the 3-Lead device.

THIS PAGE INTENTIONALLY LEFT BLANK