SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Heart Failure Monitoring System

Device Trade Name: CardioMEMS™ HF System

Device Procode: MOM

Applicant's Name and Address: CardioMEMS, Inc.

Date(s) of Panel Recommendation: December 8, 2011 & October 9, 2013

Premarket Approval Application (PMA) Number: P100045

Date of FDA Notice of Approval: May, 28, 2014

Priority Review: N/A

II. INDICATIONS FOR USE

The CardioMEMS™ HF System is indicated for wirelessly measuring and monitoring pulmonary artery (PA) pressure and heart rate in New York Heart Association (NYHA) Class III heart failure patients who have been hospitalized for heart failure in the previous year. The hemodynamic data are used by physicians for heart failure management and with the goal of reducing heart failure hospitalizations.

III. CONTRAINDICATIONS

The CardioMEMS HF System is contraindicated for patients with an inability to take dual antiplatelet or anticoagulants for one month post implant.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the CardioMEMS HF System labeling.

V. DEVICE DESCRIPTION

The CardioMEMS HF System is a permanently implantable pressure measurement system designed to provide daily PA pressure measurements including systolic, diastolic, and mean PA pressures. These measurements are used to guide treatment of congestive heart failure (CHF). The system consists of the following components:

- PA Sensor (CM3000) - The PA Sensor is a battery-free capacitive pressure sensor permanently implanted in the pulmonary artery.

- Delivery System (CM3000) – The Delivery System is a transvenous catheter designed to deploy the sensor within the distal PA. The catheter has a usable length of 120cm, has a hydrophilic coating on the distal end of the catheter, and is compatible with a 0.018" guidewire.

- CardioMEMS Hospital (CM2000) and Patient Electronics Systems (CM1000 (GSM) and CM1010 (Landline)) and Database (CardioMEMS HF Website) - The Electronics Systems acquire and process signals from the PA Sensor and transfers PA pressure measurements to a secure database. The Database receives data transmitted from the Electronics Systems, and presents the PA pressure data for review by medical professionals, who can make decisions regarding the status of the patient and initiate changes in medical therapy.

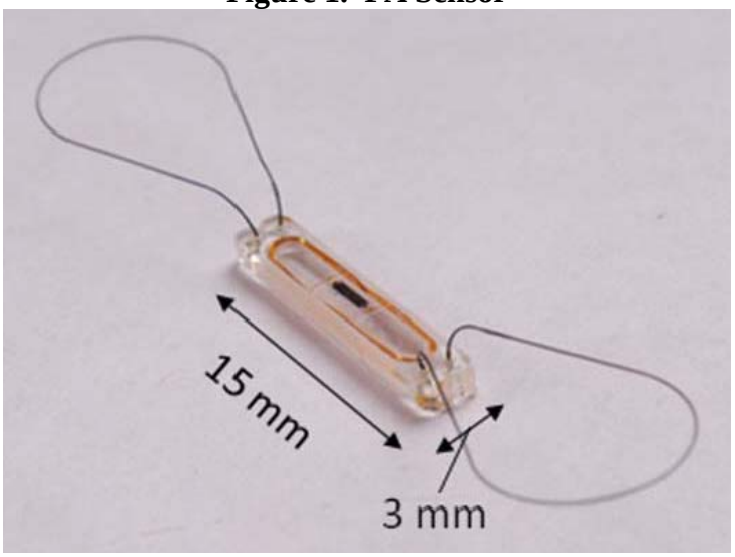
PA Sensor

The PA Sensor consists of a three (3) dimensional coil and pressure sensitive capacitor encased between two (2) wafers of fused silica measuring 15 x 3.4 x 2 mm. The fused silica assembly is completely encased in medical grade silicone. The coil electro-magnetically couples the pressure sensitive capacitor to the Electronics System, allowing the remote measurement of the resonant frequency of the circuit without the need for an on-board battery. This resonant frequency is then converted to a pressure measurement.

The sensor is implanted in a descending branch of the left or right PA using a transvenous catheter. Nitinol wire loops extend from the pressure sensor; they are larger than the sensor and keep the implant in a PA branch of substantially greater diameter than the sensor size. Two (2) platinum/iridium marker bands at each end of the sensor (total of four (4) marker bands) allow the device to be visualized under fluoroscopy during the implant procedure (and on imaging during follow-up visits) and indicate the position of the sensor. Tether wires connect the PA Sensor to the Delivery System until the physician determines that the sensor is properly positioned within the distal PA. Once the sensor is in position, the tether wires are withdrawn, releasing the sensor.

A photograph of the PA Sensor is provided in Figure 1 below.

Figure 1. PA Sensor



Delivery System

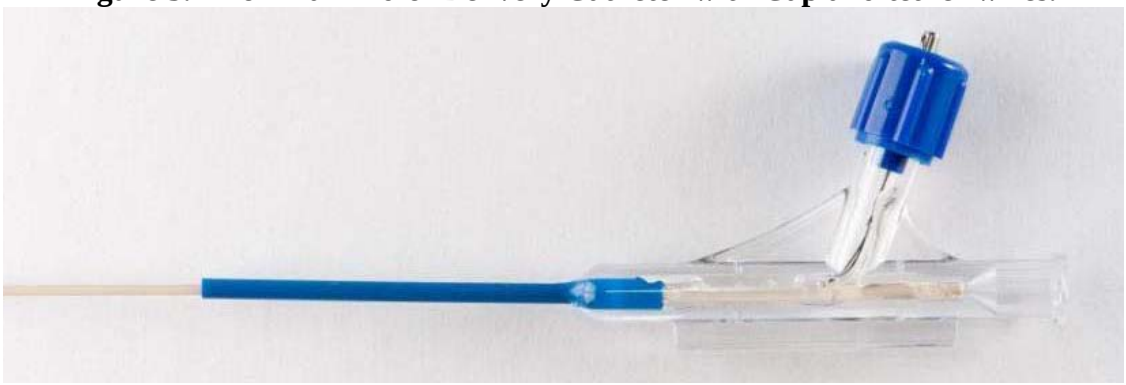
The Delivery System is an over the wire transvenous catheter used to deploy the PA Sensor. The sensor is attached by tether wires to the Delivery System as shown in Figure 2 below.

The Delivery System includes a hydrophilic coating on the distal portion of the catheter shaft. The Delivery System (with the sensor) is introduced over a guidewire through a 12Fr sheath. The usable length is 120cm and it is compatible with a 0.018" guidewire.

Figure 2. Distal Section of the PA Sensor and Delivery System including Tether Wire and Nitinol Loops.

The Delivery System is used to maneuver the sensor into the PA over the guidewire. Once it is optimally positioned, the sensor is separated from the Delivery System by pulling the tether wires that are connected to the cap on the catheter hub (see Figure 3 below). The Delivery System is then removed. The sensor remains in the PA as a permanent implant.

Figure 3. Proximal End of Delivery Catheter with Cap and tether wires.



CardioMEMS Hospital and Patient Electronics Systems and Database

The CardioMEMS HF Monitoring System consists of a Hospital Electronics System, Patient Electronics Systems, and the associated sterile PA Sensor and Delivery System. The Hospital Electronics System is used in the hospital or clinic and the Patient Electronics System is used for home patient monitoring. The hospital and patient systems are similar except for greater functionality in the hospital system including display and printing of the pressure data, which is not available on the patient version. The software for the hospital system allows pressure measurements to be visualized on the touch screen during sensor implant with systolic, diastolic, and mean PA pressure as well as a waveform. The software on the patient system prompts and guides the patient to make a PA pressure measurement and automatically uploads the information to the Database.

The physician accesses data for each of his/her patients via a secure CardioMEMS HF Website that allows the physician to utilize PA pressure measurements in the management of heart failure. When the patient is hospitalized or returns to the clinic/office setting, the Hospital Electronics System can be used to obtain PA pressure measurements and allows the physician to see not only the pressure data, but also the waveform. When the patient returns home the Patient Electronics System can be used to obtain and transmit PA pressure measurements to the Database for physician access.

There are two (2) main components in both units: the antenna and main unit.

Antenna

The antenna is used to interrogate the PA Sensor. There are two (2) versions of the antenna: a rigid plastic housing and a flat, flexible model. The rigid antenna is used during the implant procedure, while the home measurements will are made with the flat antenna which is designed to allow the patient to lie on it. During a reading, the antenna is placed in the vicinity of the passive sensor and the antenna powers it using bursts of RF energy. When the sensor is energized, it returns a signal with pressure information. This signal is received by the antenna and sent to the main unit for processing.

Main Unit

The main unit is the location of all the signal generation and processing for the Hospital and Patient Electronics Systems. The custom circuitry generates bursts of RF energy which powers the sensor, processes the return signal from the sensor, and transmits pressure information to the single board computer. This circuitry also contains barometric pressure sensors which provide information to compensate for changes in atmospheric pressure. The hospital and patient systems are similar except for greater functionality in the Hospital Electronics System including display and printing of the pressure data which is not available on the Patient Electronics System. The hospital system is illustrated in Figure 4 below.

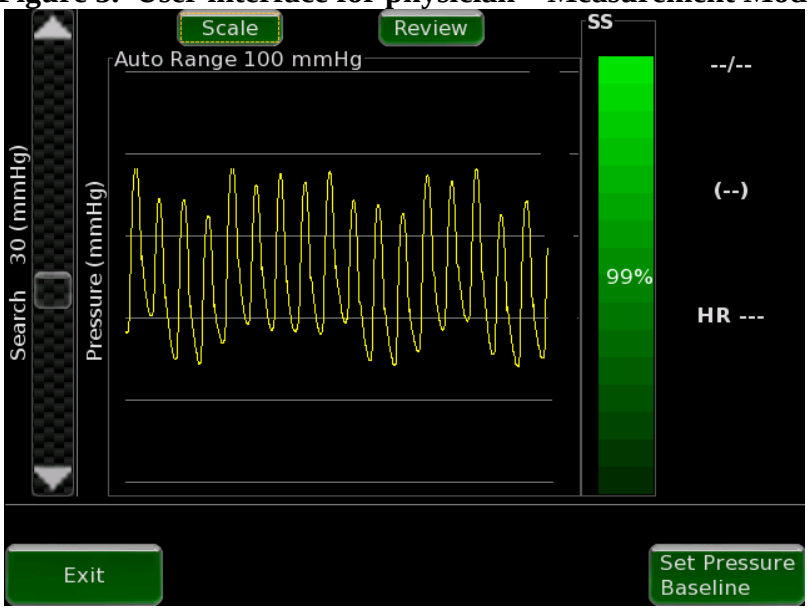
Figure 4. CardioMEMS Hospital Electronics System

Implant Procedure

Once the target vessel has been identified, the PA Sensor is deployed. A right heart catheter is then placed in the pulmonary artery to obtain pulmonary artery pressure readings for calibration of the sensor mean pressure values. Using the initial implant mode, the physician is able to collect simultaneous pressure readings with both the right heart catheter and sensor. Throughout the procedure, the physician is able to obtain any number of pressure readings.

Figure 5 below is a simulated waveform and data presentation available only for the physician during implant. The patient will see neither a waveform nor a numerical presentation of their pressure reading.

Figure 5. User interface for physician – Measurement Mode



The Hospital Electronics System can be attached to an IV pole during sensor implant. Once the implant procedure is completed, a patient system with a flexible antenna is given to the patient to take home so that they may begin transmitting pressure readings.

After the implant procedure is completed, the software will provide audio and visual prompts for the patient to guide them through signal acquisition. Once the signal is acquired, the patient is notified of the successful reading and the data is automatically transmitted to a remote secure database where the data can be evaluated by the physician.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The only alternative method for obtaining pulmonary artery pressure is currently through a right heart catheterization (RHC) procedure. This is a procedure during which a catheter is inserted through a large vein in the neck or groin and subsequently advanced into the pulmonary artery. In the hospital setting, the RHC is used to measure pulmonary artery pressure and tailor CHF therapy. However, use of this procedure to obtain pulmonary artery pressure frequently is impractical and associated with significant risks, including bruising and/or bleeding at the insertion site, trauma to the vein, trauma to the heart, and lung puncture. Other inherent risks include possible induction of cardiac arrhythmias, infection, and/or embolism.

Prior studies have concluded that changes in cardiac hemodynamics can be indicative of disease fluctuation or progression of the disease.

This alternative has its own advantages and disadvantages. A patient should fully discuss this alternative with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The CardioMEMS HF System has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Infection
  - Upper respiratory infection
  - Bronchitis
  - Pneumonia
  - Acute Bronchitis
  - Groin abscess
  - Methicilin-resistant staphylococcal aureus infection
  - Pulmonary Infiltration
  - Sepsis
- Arrhythmias
  - Ventricular tachycardia
  - Atrial fibrillation
  - Ventricular arrhythmia
  - Ventricular fibrillation
  - Atrial fibrillation with rapid ventricular response
  - Atrial flutter
  - Cardiac dysrhythmias
  - Tachycardia
  - Wide complex tachycardia
- Bleeding
  - Epistaxis
  - Hemoptysis
  - GI bleed
  - Bleeding
  - Blood in stool
  - Catheter site bleeding
  - Catheter site ecchymosis
  - Hematuria
  - Nose bleeds
- Hematoma
  - Hematoma
  - Catheter site hematoma
  - Vessel puncture site hematoma
- Thrombus
  - Arterial thrombosis (limbs)
  - Blood clot

- Myocardial infarction
- Stroke
- Transient Ischemic Attack
- Death
- Device embolization

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

Table 1. Summary of Testing- Sensor, Delivery System, and Electronics

Sensor Functional Testing			
Test	**Acceptance Criteria**	**Results**	**Analysis Type**
Sensor Accuracy	Sensor must measure within ± 2 mmHg at baseline and ± 3% across the pressure range compared to a reference pressure measurement for a pressure range of 600-860 mm Hg (absolute).	Pass	Variable
Simulated Use Pressure Cycle Conditions	Sensor must continue to function throughout 10 years of simulated fatigue testing (400 million cycles).	Pass	Attribute
	Sensor must maintain accuracy within +/- 10 mm Hg of a reference pressure measurement throughout 10 years of simulated fatigue testing (400 million cycles).	Pass	Variable
Sensor Detection Distance	Sensor must be detectable by the external measurement system at > 4” and > 50% signal strength in physiological saline.	Pass	Variable
Temperature Sensitivity	Sensor pressure measurement change per unit temperature change: +1 ± 1mm Hg / ºC.	Pass	Variable
Over-Pressure Exposure	Sensor must meet functional requirements after exposure to 2.0 atm.	Pass	Attribute
Mechanical Shock	Sensor must meet functional requirements after shock and vibration testing, per ISTA-2A.	Pass	Attribute
	Sensor must meet functional requirements after mechanical shock in testing per ISO 14708-1, part 23.1.	Pass	Attribute
Corrosion	Metallic components shall show no sign of corrosion in testing per ISO-10555-1, Annex A.	Pass	Attribute
Sensor Radiopacity	Catheter shaft is visible under fluoroscopy.	Pass	Attribute

Sensor Compatibility Testing			
Test	**Acceptance Criteria**	**Results**	**Analysis Type**
MRI	Device must meet "MR Conditional" requirements for safe scanning immediately after placement under the following conditions: - Static magnetic field of 1.5 or 3 Tesla - Maximum spatial gradient magnetic field of 720-Gauss/cm (7200-mT/m) or less In non-clinical testing with 1.5 and 3 Tesla systems, device must meet standard requirements for: - Displacement Force, per ASTM F2052-06 - RF Heating, per ASTM F2182-11 - Torque, per ASTM F2213-06 - Image Artifact, per ASTM F2119-07	Pass	Attribute -- Third Party Testing and Review
	Sensor must meet functional and accuracy requirements after 3T MR exposure.	Pass	Attribute
Defibrillation	Must meet requirements for defibrillation shock testing, per ISO 14708-1, part 20.2.	Pass	Attribute
Ultrasound	Must meet requirements of Ultrasound compatibility testing, per ISO 14708-1, part 22.	Pass	Attribute
Pacemaker and ICD Compatibility	The normal operation of the system, pacemakers, and ICD's must not be affected during simultaneous operation for potential modes of use. The in vitro test plan includes: • Representative relative placement in a human torso anatomical model • Multiple ICD and pacemaker models • Variables addressed in the test plan: o Number of pacing chambers o Potential operating modes o Unipolar and bipolar lead configurations o Relative orientations between the external system and implanted devices.	Pass	Attribute -- Third Party Testing and Review

Delivery System with Sensor			
Test	**Acceptance Criteria**	**Results**	**Analysis Type**
Simulated Implant Procedure Testing	The PA Delivery System and Sensor must meet the following requirements in simulated use testing: 1) Removal of the catheter from the packaging, 2) Catheter preparation per IFU, 3) Advancement of the catheter over the guidewire, 4) Loading of the catheter through the venous sheath, 5) Tracking over the guidewire within a venous / right heart / pulmonary arterial anatomical model, 6) Positioning the sensor in the target implant location, 7) Retraction into the sheath, 8) Sensor deployment in target location, 9) Sensor visual inspection post-delivery, 10) Catheter integrity post-removal, 11) Wire loop integrity post-removal, and 12) Sensor meets functional and accuracy requirements after simulated implant procedure.	Pass	Attribute
Catheter Shaft Tensile	Catheter shaft and hub tensile forces must be $\geq$ 15N. Test performed per ISO 10555-1, Annex B.	Pass	Variable
Hydrophilic Coating Integrity and Uniformity	$\geq$ 90% coating coverage over coated length of shaft after durability and friction test, using Congo Red dye as an indicator	Pass	Attribute -- Third Party Testing and Review
Hydrophilic Coating Durability and Friction	$\geq$ 50% reduction in friction vs. uncoated shaft, after 15 passes through silicone pads under a 500 g load.	Pass	Variable - Third Party Testing and Review
Catheter Shaft Radiopacity	Catheter shaft is visible under fluoroscopy.	Pass	Attribute
Pouch Bubble Emission Test	No continuous streams of bubbles emanating from the pouch, per ASTM F2096-11.	Pass	Attribute
Pouch Seal Tensile Test	Pouch seal peak tensile load for 1 in. wide sample must be greater $\geq$ 1.0 lbf/in, per ASTM F88-09.	Pass	Variable
Shipping and Environmental Conditions	Product must meet specifications after exposure to shipping and environmental conditions, per ISTA-2A.	Pass	Attribute
Shelf-Life	Product must meet specifications after exposure to 2-year accelerated (per Q10 Theory, per ASTM F1980-07) and real-time aging.	Pass	Attribute

Sterilization			
Test	**Acceptance Criteria**	**Results**	**Analysis Type**
Sterilization	A validated EtO sterilization process is used. It is considered an overkill sterilization cycle. The sterilization process must demonstrate a sterilization assurance level of $\leq 10^{-6}$ using a "worst case" challenge configuration of the product in a sterilization process validation performed per ISO-11135 requirements.	Pass	Attribute -- Third Party Testing and Review
Sterilization Byproducts	EtO residuals must be within acceptable limits per ISO 10993-7.	Pass	Attribute -- Third Party Testing and Review

Electronics Unit			
Test	**Acceptance Criteria**	**Results**	**Analysis Type**
Electrical Safety Testing	Electronics must meet safety requirements for medical electronic equipment defined by IEC 60601-1, AAMI ES60601-1 and CAN/CSA-C22.2 No. 60601-1.	Pass	Attribute -- Third Party Testing and Review
Emissions Testing (FCC and International)	Electronics and Sensor must meet national and international electromagnetic emissions requirements defined by IEC 60601-1-2, EN 55022, FCC Part 15 (Sensor authorization FCC identifier: R3PCSA-00051), FCC Part 18, and EN 302 510-1 & 2.	Pass	Attribute -- Third Party Testing and Review
Electromagnetic Compatibility Testing	Electronics must meet requirements for electromagnetic compatibility as defined by IEC 60601-1-2, ETSI EN 301 489-1, and ETSI EN 301 489-3.	Pass	Attribute -- Third Party Testing and Review
Design Testing	The Electronics must operate over a Frequency Range of 30 MHz to 37.5 MHz.	Pass	Attribute
	The accuracy of the system must be +/- 2mmHg at baseline and +/- 3% over the remaining operating pressure range.	Pass	Variable
	The resolution of a reading must be 1 mmHg.	Pass	Attribute
	The electrical noise must be less than 20kHz peak.	Pass	Attribute
	The sample rate shall be greater than or equal to 120 Hz.	Pass	Attribute
Thermal Assessment Test	Electronics must function accurately (within +/- 4mmHg of a reference standard) over the range of normal operating temperatures (5°C to 40°C) as defined in IEC 60601-1-11 and not exceed surface and internal temperatures as defined by IEC 60601-1.	Pass	Attribute -- Third Party Testing and Review
Flexible Antenna and Pad Set	Electronics must continue to function throughout 5 years of simulated use (1825 cycles).	Pass	Attribute

Electronics Unit			
Test	**Acceptance Criteria**	**Results**	**Analysis Type**
Verification Testing			
Mechanical Testing	Electronics must function after rough handling, shock, and vibration as defined in IEC 60601-1 and IEC 60601-1-11.	Pass	Attribute -- Third Party Testing and Review
Label Durability Testing	The labeling on the Electronics must meet durability requirements defined in IEC 60601-1.	Pass	Attribute -- Third Party Testing and Review
Ship and Environmental Testing	The Electronics shall meet transport and storage conditions defined by IEC 60601-1-11 and meet transport testing defined by ISTA-3A.	Pass	Attribute -- Third Party Testing and Review

The engineering study results for the Sensor demonstrated the following conclusions:

- Remains functional after 10 years of simulated use;
- Temperature, over-pressurization and mechanical shock have a negligible effect on Sensor function;
- Meets its specifications for accuracy during the hermeticity and calibration testing;
- Meets RF signal detection requirements for distance between the antenna and the implanted sensor in a simulation;
- Remains securely attached to the Delivery System until release;
- Is resistant to corrosion; and
- Is compatible with MRI, defibrillators, ultrasound, pacemakers and ICDs

The engineering study results for the Delivery System demonstrated the following conclusions:

- May be removed from the packaging, flushed with saline, advanced over an 0.018" guidewire and loaded into a venous sheath;
- Positions the Sensor in the target vessel, retracts into the sheath and releases the HF Sensor at the appropriate time;
- Does not damage the catheter or HF Sensor during delivery and has sufficient tensile strength to maintain its integrity during use;
- Is corrosion resistant and is sufficiently radiopaque; and
- Hydrophilic coating is durable and maintains its integrity during use.

Table 2. Biocompatibility

Test	**Acceptance Criteria**	**Results**	**Analysis Type**
Cytotoxicity	Meet requirements in an ISO Elution Method study (1xMEM Extract), per ISO 10993-5.	Pass	Attribute -- Third Party Testing

Test	Acceptance Criteria	Results	Analysis Type
Sensitization	Meet requirements in an ISO Maximization Sensitization Study (Extract), per ISO 10993-10.	Pass	Attribute -- Third Party Testing
Intracutaneous Reactivity	Meet requirements in an ISO Intracutaneous Study (Extract), per ISO 10993-10.	Pass	Attribute -- Third Party Testing
Acute and Subchronic Systemic Toxicity	Meet requirements in an ISO Systemic Toxicity Study (Extract), per ISO 10993-11.	Pass	Attribute -- Third Party Testing
Hemolysis	Meet requirements in an In Vitro Hemolysis Study (ASTM-Extraction Method), per ISO 10993-4.	Pass	Attribute -- Third Party Testing
C3a Compliment Activation	Meet requirements in a C3a Complement Activation Assay, per ISO 10993-4.	Pass	Attribute -- Third Party Testing
SC5b-9 Compliment Activation	Meet requirements in a SC5b-9 Complement Activation Assay, per ISO 10993-4.	Pass	Attribute -- Third Party Testing
USP Pryogen Study	Meet requirements in a USP Pyrogen Study (Material Mediated), per EN ISO 10993-11.	Pass	Attribute -- Third Party Testing
Chromosomal Aberration	Meet requirements in a Mouse Bone Marrow Micronucleus Study, per ISO 10993-3.	Pass	Attribute -- Third Party Testing
Bacterial Reverse Mutation	Meet requirements in a Bacterial Reverse Mutation Study (Saline Extract and DMSO Extract), per ISO 10993-3.	Pass	Attribute -- Third Party Testing
Mouse Micronucleus	Meet requirements in a Mouse Bone Marrow Micronucleus Study, per ISO-10993-3.	Pass	Attribute -- Third Party Testing
Muscle Implantation	Meet requirements in a ISO Muscle Implantation Study, per ISO-10993-6.	Pass	Attribute -- Third Party Testing
Carcinogenicity	Scientific rationale provided for no risk of carcinogenesis associated with clinical use.	Pass	Review
Chronic Toxicity, Thromboresistance, and Histopathology	Must demonstrate acceptable long term tissue response, thromboresistance, and no chronic toxicity after 12 months implantation in a porcine animal model.	Pass	Attribute -- Third Party Testing
Particulate Testing	Must meet particulate requirements per USP-788 after simulated use.	Pass	Attribute -- Third Party Testing

Table 3. US and International Standards

ISO 11607	Packaging for terminally sterilized medical Devices
ISO 14708-1, EN 45502	Active Implantable Medical Devices, General Requirements
ISTA-2A / ISTA-3A	International Safe Transit Association Medical Packaging Testing
ISO 11135	Sterilization of Health Care Products by Ethylene oxide
ISO 10993	Biological Evaluation of Medical Devices
ISO 10555-1	Sterile, Single-Use Intravascular Catheters General requirements
ASTM F2096-11	Detecting Gross Leaks in Packaging by Internal Pressurization
ASTM F88-09	Seal Strength of Flexible Barrier Materials
ASTM F1980-07	Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices
ASTM F2052-06	Measurement of Magnetically Induced Displacement Force on Medical Devices in the MR Environment
ASTM F2182-11	Measurement of RF Induced Heating on or near Passive Implants during MR Imaging
ASTM F2213-06	Measurement of Magnetically Induced Torque on Medical Devices in the MR Environment
ASTM F2119-07	Evaluation of MR Image Artifacts from Passive Implants
ISO 11607	Packaging for terminally sterilized medical Devices
EN 20594-1, EN 1707	Conical fittings with a 6% (Luer) taper
EN 980	Symbols for Medical Devices
IEC 60601-1, CAN/CSA-C22.2, ES60601-1	Medical Electrical Equipment
EN 302 510, IEC 60601-1-2, EN 301 489	Electromagnetic Compatibility
EN 55022, EN 302 510, FCC Part 18, FCC Part 15	Radiated Emissions
IEC 60601-1-11	Medical Electrical Systems in the Home Healthcare Environment
EN 62304	Life Cycle Requirements for Medical Device Software

B. Animal Studies

Chronic studies were performed in nine (9) pigs with two (2) sensors in each animal with follow-up periods of 3, 6, and 12 months. The sensors were fully endothelialized and well tolerated. Readings were obtained from all sensors throughout the studies.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

CardioMEMS, Inc. conducted a randomized, controlled pivotal study, CHAMPION, of the device under Investigational Device Exemption (IDE) application G060187. The purpose of this study was to establish a reasonable assurance of safety and effectiveness of the reduction of heart failure hospitalizations with the CardioMEMS HF System for wirelessly measuring and monitoring pulmonary artery (PA) pressure and heart rate in New York Heart Association (NYHA) Class III heart failure patients.

All subjects enrolled had the device implanted. Subjects randomized to the Treatment group were managed by their physicians using the PA pressure data. Subjects randomized to the control group had the device implanted, but data from the device was not made available to the physicians for making treatment decisions. Following completion of follow-up necessary for analysis of the primary endpoint (mean 17.6 months) (referred to as Part 1 or the Randomized Access Period), PA data was made available to physicians for all subjects, including those originally randomized to the control group. This second phase was referred to as Part 2 or the Open Access Period. CardioMEMS, Inc. continued to follow subjects enrolled in the Randomized Access Period of the Study and continued to collect data during the Open Access Period of the Study.

The Part 1 data revealed that trial conduct included subject-specific treatment recommendations sent by nurses employed by the CardioMEMS to the treating physicians. These subject-specific recommendations were limited to subjects in the treatment arm of the study. The possible impact of nurse communications was determined to severely limit the interpretability of the data in terms of effectiveness. Additionally, the *post-hoc* gender analysis noted a statistically significant treatment by gender interaction. Therefore, the evidence about device effectiveness in females is unclear.

To address these concerns, the CardioMEMS commissioned an independent third party audit to identify and characterize the nature of all communications between CardioMEMS and the investigative sites. CardioMEMS also continued to follow patients implanted with the device in Part 2 (Open Access Period). The results of the audit were found to be acceptable. Notably, the audit results provided assurance that the nurse communications were limited to Part 1 (Randomized Access Period) of the study. CardioMEMS provided a Clinical Analysis that included a clinical evaluation of the nurse communications to assess the clinical impact on Heart Failure Related (HFR) hospitalizations. Finally, CardioMEMS conducted multiple analyses of the Part 2 data in order to demonstrate that the observed effect could be attributed to the device and not only to the nurse communications with investigational sites.

A. Study Design

Randomized Access (Part 1)

For the initial Randomized Access Period of the Study (Part 1), patients were treated between September 6, 2007 and August 12, 2010. The database for this PMA reflected data collected through April 30, 2012 and included 550 patients. There were 64 investigational sites.

The study was a prospective, multi-center, randomized, single-blind clinical trial conducted in the United States (US). All subjects who met the eligibility criteria at the Screening Visit and provided informed consent form were eligible to participate within the study. Following the Screening Visit, all subjects were implanted in conjunction with a right heart catheterization (RHC) procedure. Following the RHC and after sensor implant, but prior to hospital discharge, subjects were randomized to one of two (2) groups:

- Treatment group: standard of care HF management plus HF management based upon hemodynamic information obtained from the HF System
- Control group: standard of care HF management

Following the Sensor implant, subjects were hospitalized overnight for observation and evaluation. Prior to hospital discharge, subjects were trained in the use of the equipment, including how to take their daily HF pressure measurements and how to initiate the transfer of their pressure reading to a secure database.

For the Treatment group, the investigator provided standard of care HF management plus HF management based upon hemodynamic information obtained from the HF System. If the PA pressures were outside the prescribed limits, the investigator used the data in their evaluation of the medical condition of the patient and initiated treatment options per recommendations specified within the clinical protocol.

For the Control group, the investigator provided standard of care HF management and did not have access to the home pressure measurements.

All subjects were blinded to the randomization assignment and did not have access to their pulmonary artery pressures.

During the study, patient contact by the investigative sites by phone was scripted for both Treatment and Control groups. The script for both groups was identical except for the medication adjustment in the Treatment group. The contact was balanced to assure that when a Treatment patient was contacted by phone for a PA pressure based intervention, a matching phone contact was made to a randomly selected control patient.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the CHAMPION study was limited to patients who met the following inclusion criteria:

- Written informed consent obtained from subject or legal representative.
- Male or female, at least 18 years of age
- Diagnosis of HF ≥ 3 months, with either preserved or reduced Left Ventricular Ejection Fraction (LVEF)
- Diagnosis of NYHA Class III HF (historical assessment documented at screening visit)
- At least one HF-related hospitalization within 12 months of Screening Visit
- Subjects with reduced LVEF must be receiving a beta blocker for three (3) months and an Angiotensin-Converting Enzyme Inhibitor (ACE-I) or Angiotensin Receptor Blocker (ARB) for one (1) month unless in the investigator's opinion, the subject is intolerant to beta blockers, ACE-I, or ARB. Beta blockers and ACE-I (or ARB) doses should be stable for one (1) month prior to study entry.
- Subjects with a BMI ≤ 35 or chest circumference ≤ 52 inches. In subjects with BMI >35 and chest circumference > 52 inches, the distance from the subject's back to the pulmonary artery must be < 10 cm on lateral angiography during the RHC. Patients with chest circumference > 65 inches were excluded.
- Subjects with implant pulmonary artery branch diameter between 7mm and 15mm.
- Female subjects of childbearing age with a negative urine or serum pregnancy test (at Screening Visit), and who have agreed to use a reliable mechanical or hormonal form of contraception during the study will be allowed to enter the study. Note: A female is considered of child-bearing potential unless she is postmenopausal for two (2) years, has had a total hysterectomy, or has had a bilateral tubal ligation.
- Subjects willing and able to comply with the follow up requirements of the study.

Patients were not permitted to enroll in the CHAMPION study if they met any of the following exclusion criteria:

- Subjects with an active infection.
- Subjects with history of recurrent (>1) pulmonary embolism or deep vein thrombosis.
- Subjects, in the investigator's opinion, unable to tolerate a right heart catheterization.
- Subjects who have had a major cardiovascular event (e.g., myocardial infarction, stroke) within two (2) months of Screening Visit.
- Subjects with Cardiac Resynchronization Device (CRT) implanted ≤ 3 months prior to enrollment.

- Subjects with a Glomerular Filtration Rate (GFR) <25 ml/min who are non-responsive to diuretic therapy or who are on chronic renal dialysis.
- Subjects likely to undergo heart transplantation within six (6) months of Screening Visit.
- Subjects with congenital heart disease or mechanical right heart valve(s).
- Subjects with known coagulation disorders.
- Subjects with a hypersensitivity or allergy to aspirin, and/or clopidogrel.
- Subjects enrolled in concurrent studies that may confound the results of this study.
- Subjects whose clinical condition, in the investigator's opinion, would not allow them to complete the study.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 1, 3, and 6 months and every 6 months thereafter. Table 4 identifies preoperative and postoperative evaluations and timeframes for study subjects. Adverse events and complications were recorded at all visits

Table 4. Schedule of Events

	Screening	Baseline	Month 1	Month 3	Month 6	Every 6 Months or Study Termination
Procedures	Visit 1	Visit 2 Sensor Implant (≤ 2 weeks of Visit 1)	Visit 3 (30 ± 7 days)	Visit 4 (90 ± 14 days)	Visit 5 (180 ±14 days)	Visits 6-10 or until marketing approval (± 30 day window)
Informed Consent	X					
Serum or Urine Pregnancy Test	X[1]					
Demographics	X					
Past Medical & Surgical History	X					
Blood Chemistry (Creatinine)	X				X	
Inclusion/Exclusion Criteria Review	X	X[2]				
GFR	X					
INR (if indicated)		X				
Swan-Ganz measurement		X				
Physical Examination (including weight)	X[3]	X (Abbreviated PE)[3]	X[3]	X[3]	X[3]	X[3]

	Screening	Baseline	Month 1	Month 3	Month 6	Every 6 Months or Study Termination
NYHA HF Classification	X	X	X	X	X	X
QOL questionnaire (Minnesota)	X		X	X	X	X (12 month only)
SF-12 Survey	X		X	X	X	X (12 month only)
EQ-5D Instrument	X		X	X	X	X (12 month only)
Randomization		X				
Pulmonary Artery Angiography		X[4]				
Sensor Implant		X				
Sensor Measurements		X[5]				
HF Sensor Support Questionnaire	X					
Adverse Events Assessment		X	X	X	X	X
Medication	X	X	X	X	X	X
Phone Contact			As needed[6]	As needed[6]	As needed[6]	As needed[6]

[1]Females of child bearing potential

[2]Review of clinical laboratory findings against clinical laboratory inclusion/exclusion criteria for eligibility verification

[3]Include weight, height and vital signs (temperature, blood pressure, pulse, respirations). BASELINE: Abbreviated Physical Exam (i.e., weight, vital signs and significant changes since Screening)

[4]Subjects with BMI > 35 and chest circumference between 52" and 65", need to have appropriately located pulmonary artery branch (defined as < 10 cm from the pulmonary artery branch to the skin of the back) prior to implant procedure as measured by angiography at the Baseline Visit will receive the Sensor implant.

[5]Sensor measurements will be performed for both groups of subjects, however the control group's measurements will be blinded to the physician to better reflect standard of care.

[6]Refer to section 6.1.10 of the clinical protocol

3. Clinical Endpoints

With regards to safety, the primary safety endpoints were tested hierarchically, in order to control for multiplicity. Employing the O'Brien Fleming analysis methodology for one (1) interim analysis, the primary safety analysis nominal significance level was set at 0.048 for the final analysis. First, the freedom from device/system-related complication (DSRC) rate was tested. If the result was statistically significant (i.e., $p \leq 0.048$), then the freedom from pressure sensor failure rate was also tested for significance (i.e., $p \leq 0.048$). The study was

judged to have provided positive safety results if both tests of the primary safety analysis endpoints were statistically significant (i.e., $p \leq 0.048$).

Analysis of DSRC was based on the following objective performance criteria: the lower limit of the two-sided 95.2% confidence interval on the freedom from DSRC rate for the combined patient groups at six (6) months was at least 80%. The statistical hypotheses were:

H_0: $\pi_{\text{(Freedom from device } I \text{ system-related complications at six months)}} \leq 80\%$
H_1: $\pi_{\text{(Freedom from device } I \text{ system-related complications at six months)}} > 80\%$

Analysis of sensor failures was based on the following objective performance criteria: the lower limit of the two-sided 95.2% confidence interval on the freedom from pressure sensor failure rate for the combined patient groups at six (6) months was at least 90%. The statistical hypotheses were:

H_0: $\pi_{\text{(Freedom from pressure sensor failure at six months)}} \leq 90\%$
H_1: $\pi_{\text{(Freedom from pressure sensor failure at six months)}} > 90\%$

With regards to effectiveness, employing the O'Brien Fleming analysis methodology for one (1) interim analysis, the primary efficacy analysis nominal significance level was set at 0.048 for the final analysis. The study was judged to have provided positive efficacy results if the final efficacy result was statistically significant (i.e., $p \leq 0.048$) using the negative binomial regression procedure. The primary alternative hypothesis of interest was that the Treatment group (standard of care HF management plus HF management based upon hemodynamic information obtained from the CardioMEMS HF System) will have a lower rate of HF hospitalizations at 6 months than the control group (standard of care HF management only). The statistical hypotheses were:

H_0: $\mu_{(\text{Treatment Group})} = \mu_{(\text{Control Group})}$
H_a: $\mu_{(\text{Treatment Group})} \neq \mu_{(\text{Control Group})}$

where, μ is the rate of heart failure-related hospitalizations through six (6) months.

Additionally, there were four (4) secondary effectiveness endpoints analyzed at the six (6) month visit. The statistical analysis tested the secondary effectiveness endpoints according to a hierarchical strategy in order to preserve an overall Type I error rate of 5%. These secondary effectiveness endpoints included:

- Change from baseline in PA mean pressures;
- Proportion of patients hospitalized for heart failure;
- Days alive outside of the hospital; and
- Quality of Life – Minnesota Living with Heart Failure Questionnaire (MLHFQ).

An interim analysis was conducted by the Data Safety Monitoring Board (DSMB) after 50% of the subjects completed at least six (6) months on study (or prematurely discontinued).

Supplementary Analyses were performed on the full duration of follow-up data (12 months) (Part 1) and included:

- analyzing the primary safety endpoints and effectiveness endpoints over the whole study duration;
- analyzing the effectiveness endpoints under the per-protocol population where some subjects were excluded; and
- performing survival analyses to compare the survival curves and HFR hospitalization free survival curves between the treatment group and the control group.

Open Access (Part 2)

For the Open Access Period, patients were treated between August 12, 2010 and April 30, 2012. The database for this PMA reflected data collected through April 30, 2012 and included 347 patients. There were 64 investigational sites.

Following the completion of the period of Randomized Access (Part 1), the investigators continued to receive PA pressure data for Treatment group subjects, and began to receive PA pressure data for Control group subjects. In other words, subjects in Part 1 transitioned to a period of Open Access, defined as the Part 2 of the study. During Part 2, investigators received automated alerts and had access to subject PA pressure measurements for all subjects (both Treatment and Control groups) but received no CardioMEMS nurse subject-specific treatment recommendations as established by an independent third party audit.

A series of ancillary analyses were used to evaluate outcomes when all subjects' investigators received access to PA pressure information during Part 2 of the study. Part 2 study results were compared to Part 1. Specifically, the longitudinal analyses (Open Access Part 2), discussed below, focused on the changes in the HFR hospitalizations as the subjects transitioned from Part 1 to Part 2. Table 5 below outlines the differences between the study periods, randomized groups, and study components.

Table 5. Distinctions for Part 1 (Randomized Access) and Part 2 (Open Access).

Study Period	Randomized Group	Study Component		
		Standard of Care Heart Failure Management	Physician Knowledge of PA Pressures	Nurse Communications to Enhance Protocol Compliance
Randomized Access (Part 1)	Treatment	Yes	Yes	Yes
	Control	*Yes*	*No*	*No*
Open Access (Part 2)	*Former Control*	*Yes*	*Yes*	*No*
	Former Treatment	Yes	Yes	No

1. Clinical Inclusion and Exclusion Criteria
   The Inclusion and Exclusion Criteria did not change from Part 1.

2. Follow-up Schedule
   All patients continued to be followed per the protocol. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints
   The longitudinal analyses were based on the Randomized Access Period of the Study (Part 1) and Open Access Period of the Study (Part 2). The Randomized Access (Part 1) focused on the differences in the rate of HFR hospitalization between Treatment and Control groups. The longitudinal analyses compared the rate of HFR hospitalization in subjects followed during the Open Access (Part 2). These longitudinal analyses were designed to further evaluate whether knowledge of PA pressures, un-confounded by nurse communications, reduced the rate of HFR hospitalizations.

   CardioMEMS analyzed an intent-to-treat (ITT) population, which consisted of all subjects who were randomized into the study, regardless of study completion status. Subjects who were lost-to-follow-up, underwent VAD implantation or heart transplantation, withdrew consent or died were censored at the time of occurrence of these events. Censoring these subjects excluded the subject's subsequent events after the censoring from the analyses. CardioMEMS proposed the Anderson-Gill multiplicative hazards model to accommodate variable follow-up times as well as recurrent heart failure events using the combined Part 1 and Part 2 longitudinal data. CardioMEMS used an Anderson-Gill model with Frailty, which allows for random effects, to address the correlated data.

   To assess the effect of using PA pressure measurements to guide medical therapy to prevent HFR hospitalizations, and to establish device effectiveness among females, four (4) analyses were performed: Longitudinal, Gender, Propensity, and Clinical. P-values should be interpreted with caution because the analyses including Part 2 data were not specified before the onset of the study and there are

various sources of confounding effects which cannot be separated from the treatment effect. Each analysis is briefly described below.

a. Longitudinal Analyses

i. Comparison of Former Control (Part 2) to Control (Part 1): To determine whether the HFR hospitalization rate was lower in the Former Control group than the Control group, when physicians of Former Control patients received access to PA pressures (neither had nurse communications).

ii. Comparison of Former Treatment (Part 2) to Treatment (Part 1): To evaluate whether HFR hospitalization rates remain the same in subjects whose physician's access to PA pressures remained unchanged, but no longer received nurse communications.

iii. Comparison of Former Control (Part 2) to Former Treatment (Part 2): To demonstrate that the rates of HFR hospitalizations were similar during Part 2 when both groups were managed in an identical fashion (access to PA pressure and no nurse communications).

iv. Change in HFR Hospitalization Rates in the Control group (Part 2 vs. Part 1) compared to the Change in HFR Hospitalization Rates in the Treatment Group (Part 2 vs. Part 1): To demonstrate that the magnitude of change in HFR hospitalization rates after the transition from Control to Former Control (Part 1 vs. Part 2, initiation of physician access to PA pressures in Part 2) was greater than the magnitude of change in HFR hospitalization rates after the transition from Treatment to Former Treatment (Part 1 vs. Part 2, no change in physician access to PA pressure).

CardioMEMS proposed the Anderson-Gill multiplicative hazards model to accommodate variable follow-up times as well as recurrent events using the combined Part 1 and Part 2 longitudinal data. An additional random variable, $w_{i,}$ was added to the model to account for the level of frailty, where the log-frailty random variable has a normal distribution with mean zero and unknown variance σ^2. The model of the hazard rate for the i^{th} subject, i=1,…, n, is structured as follows:

$$\lambda_i(t) = \lambda_0(t)\exp\{\beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3i} + \gamma w_i\}$$

$$X_1 = \begin{cases} 1 & Treatment\ Group \\ 0 & Control\ Group \end{cases}$$

$$X_2 = \begin{cases} 1 & if\ t \epsilon Part\ 2 \\ 0 & if\ t \epsilon Part\ 1 \end{cases}$$

$$X_3 = X_1 \cdot X_2 = \begin{cases} 1 & if\ X_1{=}1\ (Treatment\ Group)\ and\ X_2{=}1\ (Part\ 2) \\ 0 & otherwise \end{cases}$$

CardioMEMS performed multiple supporting analyses to evaluate the assumptions and robustness including:

- Proportional Hazards and Independence of the Recurrent Hospitalization used in the A-G model;
- Robustness of the A-G model including GEE models, non-parametric methods and non-parametric bootstrapping procedures;
- Longitudinal analyses using individual data from Part 1 and Part 2;
- Competing risk analysis to assess the impact of death when it is considered an event;
- Covariate adjusted analysis; and
- Analysis to evaluate missing data.

b. Gender Analysis

An ancillary subgroup analysis of 6 month HFR hospitalization based on gender was performed in an effort to address the issues raised regarding the Randomized Access Period of the Study (Part 1) gender analysis. The initial gender analysis was a *post hoc* analysis, which compared HFR hospitalization rates between males and females in the Treatment and Control groups. The initial gender analysis noted a statistically significant treatment by gender interaction. In order to examine whether the treatment-by-gender interaction was driven by early deaths in the Control group females, the composite endpoint of "death or first HFR hospitalization" was analyzed using a Cox proportional hazard model over Part 1 and the full duration of Part 1 plus Part 2. The concern was that death had created a significant competing risk problem in the Control group women and therefore led to lower HFR hospitalization rates, since early death precludes the possibility of further HFR hospitalizations. In addition, the endpoints of time to first HFR hospitalization over Part 1 and over full Duration Part 1 plus Part 2 were assessed in the Cox proportional hazard model.

To demonstrate the robustness of the findings, CardioMEMS performed the composite endpoints of recurrent HFR hospitalization or death (death is treated as a HFR hospitalization) over Part 1 and over full Duration Part 1 + Part 2 using Andersen-Gill model with robust sandwich estimates, Anderson-Gill model with Frailty and using the Negative Binomial Regression.

c. Propensity Analysis

Part 1 results were analyzed after excluding all Treatment group subjects whose treating investigators received a patient-specific CardioMEMS nurse recommendation. In order to have an adequate Control group for this analysis, a Propensity Score model was developed prior to any final data analysis. The Treatment group (N=270) was divided based on whether the study subjects were the topic of a nurse communication. Those patients in the Treatment group who

were never the topic of a nurse communication were placed in the Treatment No Nurse Communications (TNNC) group (N=99). The propensity modeling, using one-to-one nearest neighbor approach, matched the cohort of TNNC group with a comparable group of subjects in the Control group (N=99). An independent statistician evaluated and included the baseline variables in the final propensity model, using backward elimination, with the threshold for retaining a variable in the model at $p<0.3$. A Propensity Model with all covariates forced into the model was also considered. The propensity score was calculated using logistic regression with a treatment indicator as the outcome variable. The treatment indicator identified whether a patient belonged to the TNNC group or the Control group.

Based on the two (2) propensity score models, 30 sets of matched data were generated. These sets were generated to explore the robustness of the matching due to the dependency of the matching procedure on the sorting order. Each matched data set has a different random sorting of the 99 TNNC participants prior to the matching and 99 matched participants in the Control group based on their estimated propensity scores. For each matched data set, the independent statistician identified and quantified the potential imbalance that existed between the two (2) groups prior to performing the propensity score modeling. The approaches that evaluated the potential imbalances included Wilcoxon rank sum tests, variance ratios, standardized differences in performance, quantile-quantile (Q-Q) plots, and distribution plots for continuous variables; Fisher's Exact test, and observed proportions were used for categorical variables.

The final propensity model and the matched data were provided to a separate and independent 3rd party data analysis center for the outcome analysis, i.e. 6 month HFR hospitalization rates (the same as the pre-specified primary effectiveness endpoint).

d. Clinical Analysis

The clinical impact of the nurse communications with the goal of identifying and discussing the potential influence on the rate of HFR hospitalization was assessed. Two (2) cardiologists, acting independently of each other, with expertise in HF and clinical trials and who had not been involved in the design, recruitment, execution, or initial analysis of the CHAMPION study, performed the clinical analyses. These two (2) cardiologists identified and reviewed every email and logged phone communication between CardioMEMS and the investigators. A nurse communication was defined as potentially providing a treatment recommendation if the text of the communication referred to the potential desirability of, or the need for, a change in a specific type of medication or treatment, regardless of whether the text referred to a class of drug, a specific agent by name, or a specific dose or specific route of administration. A treatment recommendation and a medication change were considered 'concordant' if the medication change took place within a specified period of having received the

nurse communication. The analysis was conducted using four (4) different concordance time periods (0-1, 0-2, 0-3, and 0-7 days). Furthermore, the medication change was labeled as 'consistent' or 'not consistent' with the study protocol. The cardiologists classified the nurse communications as either:

- Concordant use of drugs consistent with study protocol and hypothesis.
- Concordant use of drugs not consistent with study protocol and hypotheses.
- No concordant medication change.

After classification, the cardiologists estimated the percentage of the treatment effect that may have been related to nurse communications.

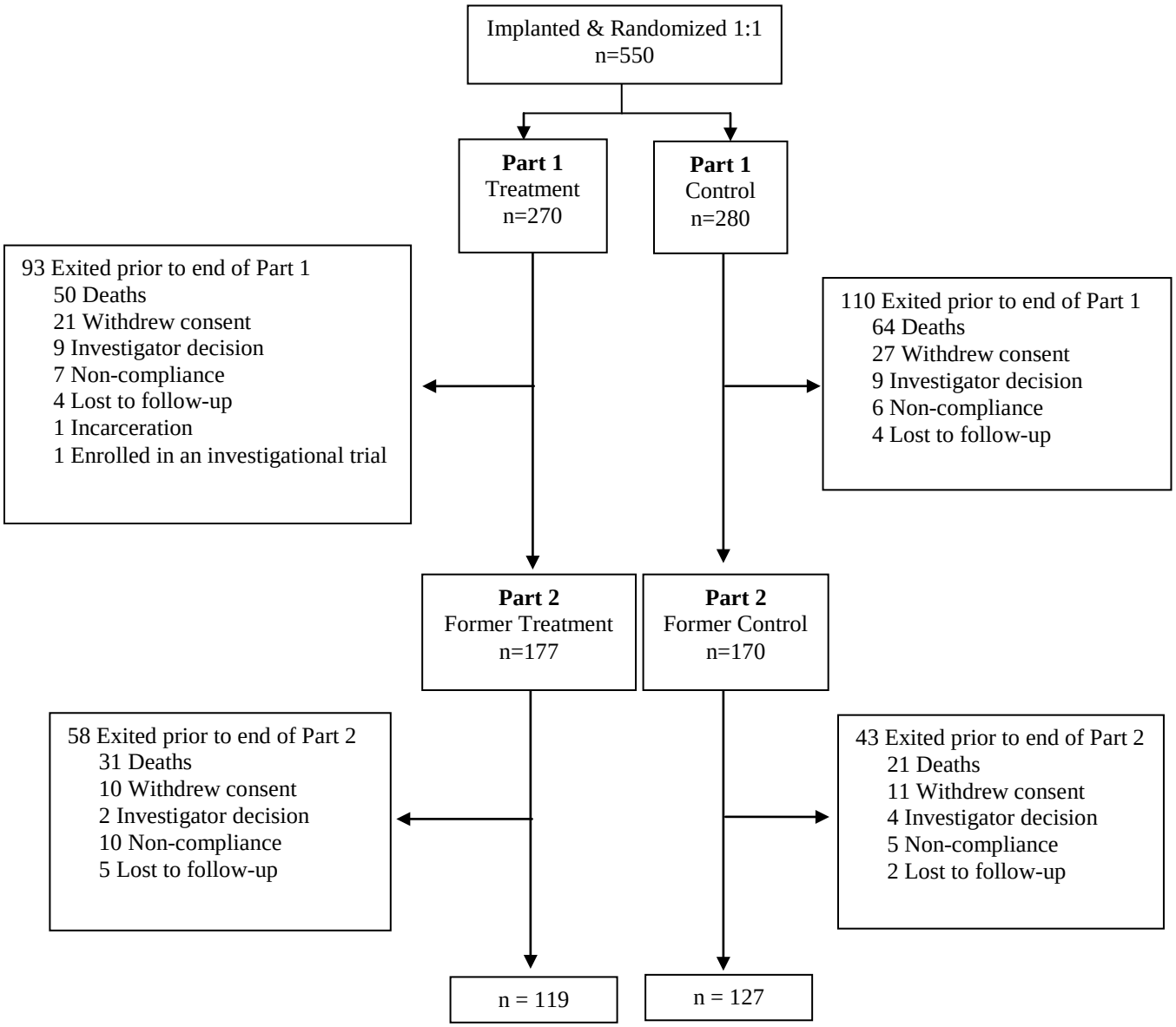
Importantly, this analysis also served to establish the appropriate time point after which the data should not be considered potentially biased by nurse communications.

B. Accountability of PMA Cohort

At the time of database lock, a total of 550 subjects were implanted with the device and then randomized 1:1 to either the Treatment group (n=270 subjects) or to the Control group (n=280 subjects). A total of 347 subjects (177 in the Treatment group and 170 in the Control group) completed the full period of Randomized Access (Part 1). During the course of Part 1, 93 subjects in the Treatment group and 110 subjects in the Control group exited for reasons described in Figure 6 below. The average duration of follow-up for Part 1 was 533.5 days in the Treatment group and 524.7 days in the Control group. For Part 2, the average duration of follow-up was 372.7 days in the Former Treatment group and 405.4 days in the Former Control group.

Subject demographics and medical history were reasonably matched between the Treatment and Control groups in Part 1 and between the Former Treatment and Former Control in Part 2 in regard to their original baseline characteristics which were measured prior to the onset of Part 1.

Figure 6. Patient Disposition



Additionally, Table 6 shows an assessment of the deaths that occurred in Part 1 and Part 2 of the study. There was a relative reduction in the death rate of 29% ((17.5% - 12.4%) ÷ 17.5%) comparing the Former Control group to the Former Treatment group.

Table 6. Deaths Occurring in Part 1 and Part 2

	Part 1	Part 2
Deaths in Treatment Arm	50/270 (18.5%)	31/177 (17.5%)
Cardiac	40/270 (14.8%)	25/177 (14.1%)
Non-Cardiac	10/270 (3.7%)	6/177 (3.4%)
Deaths in Control Arm	64/280 (22.9%)	21/170 (12.4%)
Cardiac	49/280 (17.5%)	17/170 (10.0%)
Non-Cardiac	15/280 (5.3%)	4/170 (2.4%)

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a heart failure study performed in the US.

Patient Demographics for Part 1 and Part 2

Table 7 includes the patient demographics at the time of enrollment for the Randomized Access (Part 1). Table 8 includes the patient demographics as patients transferred into the Open Access (Part 2).

Table 7. Part 1 Population Demographics and Baseline Parameters

Variables	Randomized Group		p-value[1]
	Treatment (N=270)	Control (N=280)	
Age (years)	61.3 ± 12.98 (270)	61.8 ± 12.73 (280)	0.5927
Male	194/270 (71.9%)	205/280 (73.2%)	0.7745
Race (White)	196/270 (72.6%)	205/280 (73.2%)	0.9236
Systolic BP (mmHg)	121.2 ± 22.52 (270)	123.2 ± 21.01 (280)	0.1286
Heart Rate (bpm)	72.4 ± 12.91 (269)	73.0 ± 12.14 (280)	0.4873
BMI	30.5 ± 6.50 (270)	30.9 ± 7.35 (280)	0.6228
BUN (mg/dL)	29.6 ± 17.99 (248)	28.1 ± 16.17 (267)	0.6325
Creatinine (mg/dL)	1.4 ± 0.47 (270)	1.4 ± 0.42 (280)	0.5560
GFR (mL/min/1.73m²)	60.4 ± 22.50 (270)	61.8 ± 23.20 (280)	0.5638
Ejection Fraction (EF>=40%)	62/270 (23.0%)	57/279 (20.4%)	0.5343
Cardiac Output (L/min)	4.5 ± 1.41 (270)	4.6 ± 1.54 (278)	0.5499
Cardiac Index (L/min/m²)	2.1 ± 0.59 (270)	2.2 ± 0.64 (278)	0.4405
PVR	2.9 ± 2.02 (270)	2.7 ± 1.82 (278)	0.4609
PA Wedge Pressure (mmHg)	17.5 ± 7.97 (270)	19.0 ± 8.12 (280)	0.0276
PA Mean Pressure (mmHg)	28.9 ± 9.92 (270)	29.9 ± 10.05 (280)	0.3021

Variables	Randomized Group		p-value[1]
	Treatment (N=270)	Control (N=280)	
CRT-D/ICD Implant	179/270 (66.3%)	197/280 (70.4%)	0.3145
Ischemic Cardiomyopathy	158/270 (58.5%)	174/280 (62.1%)	0.4327
Hypertension	207/270 (76.7%)	220/280 (78.6%)	0.6100
Hyperlipidemia	204/270 (75.6%)	218/280 (77.9%)	0.5458
Coronary Artery Disease	182/270 (67.4%)	202/280 (72.1%)	0.2290
History of MI	134/270 (49.6%)	137/280 (48.9%)	0.9320
Diabetes Mellitus	130/270 (48.1%)	139/280 (49.6%)	0.7337
AFIB	120/270 (44.4%)	135/280 (48.2%)	0.3932
COPD	76/270 (28.1%)	83/280 (29.6%)	0.7078
ACE/ARB use	205/270 (75.9%)	222/280 (79.3%)	0.3584
Beta Blocker use	243/270 (90.0%)	256/280 (91.4%)	0.6595

[1] Wilcoxon Rank-Sum Test for continuous measures and Fisher's exact test for categorical measures.

Table 8. Part 2 Population Demographics and Baseline Parameters

Variables	Group		p-value[1]
	Former Treatment (N=177)	Former Control (N=170)	
Age (years)	60.5 ± 12.14 (177)	60.0 ± 12.78 (170)	0.8506
Male	123/177 (69.5%)	119/170 (70.0%)	1.0000
Race (White)	123/177 (69.5%)	119/170 (70.0%)	1.0000
Systolic BP (mmHg)	121.8 ± 22.85 (177)	123.4 ± 19.98 (170)	0.2815
Heart Rate (bpm)	71.2 ± 11.55 (177)	71.6 ± 11.48 (170)	0.7648
BMI	31.1 ± 6.41 (177)	31.6 ± 7.56 (170)	0.6047
BUN (mg/dL)	27.8 ± 16.85 (162)	26.2 ± 13.70 (159)	0.7724
Creatinine (mg/dL)	1.4 ± 0.44 (177)	1.3 ± 0.41 (170)	0.7778
GFR (mL/min/1.73m²)	61.8 ± 22.33 (177)	63.2 ± 23.63 (170)	0.6676
Ejection Fraction (EF>=40%)	44/177 (24.9%)	39/169 (23.1%)	0.7076
Cardiac Output (L/min)	4.6 ± 1.34 (177)	4.8 ± 1.48 (168)	0.2931
Cardiac Index (L/min/m²)	2.2 ± 0.58 (177)	2.3 ± 0.60 (168)	0.1324
PVR	2.6 ± 1.73 (177)	2.4 ± 1.66 (168)	0.2451

Variables	Group		p-value[1]
	Former Treatment (N=177)	Former Control (N=170)	
PA Wedge Pressure (mmHg)	16.8 ± 8.31 (177)	17.5 ± 8.25 (170)	0.3556
PA Mean Pressure (mmHg)	27.9 ± 10.23 (177)	28.0 ± 9.92 (170)	0.8322
CRT-D/ICD Implant	112/177 (63.3%)	113/170 (66.5%)	0.5745
Ischemic Cardiomyopathy	102/177 (57.6%)	97/170 (57.1%)	1.0000
Hypertension	139/177 (78.5%)	135/170 (79.4%)	0.8955
Hyperlipidemia	133/177 (75.1%)	133/170 (78.2%)	0.5272
Coronary Artery Disease	115/177 (65.0%)	112/170 (65.9%)	0.9103
History of MI	87/177 (49.2%)	76/170 (44.7%)	0.4517
Diabetes Mellitus	87/177 (49.2%)	83/170 (48.8%)	1.0000
AFIB	71/177 (40.1%)	71/170 (41.8%)	0.8272
COPD	47/177 (26.6%)	54/170 (31.8%)	0.2905
ACE/ARB use	142/177 (80.2%)	140/170 (82.4%)	0.6802
Beta Blocker use	163/177 (92.1%)	159/170 (93.5%)	0.6804

[1] Wilcoxon Rank-Sum Test for continuous measures and Fisher's exact test for categorical measures.

Table 9 summarizes the duration of patient participation during the trial. For the Randomized Access Study (Part 1), the average duration of follow-up was 533.5 days in the Treatment group and 524.7 days in the Control group. For the Open Access Study (Part 2), the average duration of follow-up was 372.7 days in the Former Treatment group and 405.4 days in the Former Control group. The total number of patient years was 797 for Part 1 and 1,166 for Part 1 + Part 2 combined.

Table 9. Patient Follow Up Duration (Days) in Study: Part 1 & Full Study Duration

	Treatment (270)	Control (280)	All Patients (550)
Part 1 Follow-up (days)			
Mean±StdDev (N)	533.5±236.9 (270)	524.7±231.8 (280)	529.0±234.1 (550)
Median	521.5	524.5	523.0
(Min, Max)	(4, 1,036)	(1, 1,010)	(1, 1,036)
Total Patient Days	144,054	146,910	290,964
Part 1 + Part 2 Follow-up (days)			
Mean±StdDev (N)	777.9±353.3 (270)	770.8±353.3 (280)	774.3±353.0 (550)
Median	951.0	946.0	949.5
(Min, Max)	(4, 1,258)	(1, 1,308)	(1, 1,308)

	Treatment (270)	Control (280)	All Patients (550)
Total Patient Days	210,022	215,821	425,843

Patient Duration (Days) in Study: Part 2

	Former Treatment (177)	Former Control (170)	All Patients (347)
Part 2 Follow-up (days)			
Mean±StdDev (N)	372.7±182.6 (177)	405.4±187.8 (170)	388.7±185.6 (347)
Median	345.0	397.0	372.0
(Min, Max)	(31, 662)	(25, 662)	(25, 662)
Total Patient Days	65,968	68,911	134,879

A pre-specified analysis on the background Heart Failure Medical Therapy was performed, as shown in Tables 10 and 11. The p-values in the table were not adjusted for multiplicity.

Table 10. Baseline HF Drug Therapy

HF Medication	Treatment (270)	Control (280)	All Patients (550)	p-value[1]
ACE/ARB	205 (75.9%)	222 (79.3%)	427 (77.6%)	0.3584
Beta Blocker	243 (90.0%)	256 (91.4%)	499 (90.7%)	0.6595
Aldosterone Antagonist	117 (43.3%)	114 (40.7%)	231 (42.0%)	0.5463
Nitrate	64 (23.7%)	56 (20.0%)	120 (21.8%)	0.3035
Hydralazine	36 (13.3%)	33 (11.8%)	69 (12.5%)	0.6084
Diuretic-Loop	248 (91.9%)	258 (92.1%)	506 (92.0%)	>0.9999
Diuretic-Thiazide-Standing	30 (11.1%)	35 (12.5%)	65 (11.8%)	0.6922
Diuretic-Thiazide-PRN	20 (7.4%)	18 (6.4%)	38 (6.9%)	0.7374

[1]p-value testing Treatment vs. Control obtained from Fisher's Exact Test.

Table 11. HF Drug Therapy at 6 months

HF Medication	Treatment (270)	Control (280)	All Patients (550)	p-value[1]
ACE/ARB	203 (75.2%)	213 (76.1%)	416 (75.6%)	0.8428
Beta Blocker	236 (87.4%)	246 (87.9%)	482 (87.6%)	0.8975
Aldosterone Antagonist	130 (48.1%)	124 (44.3%)	254 (46.2%)	0.3926
Nitrate	113 (41.9%)	65 (23.2%)	178 (32.4%)	<0.0001
Hydralazine	61 (22.6%)	42 (15.0%)	103 (18.7%)	0.0285
Diuretic-Loop	239 (88.5%)	251 (89.6%)	490 (89.1%)	0.6840
Diuretic-Thiazide-Standing	53 (19.6%)	41 (14.6%)	94 (17.1%)	0.1407
Diuretic-Thiazide-PRN	33 (12.2%)	30 (10.7%)	63 (11.5%)	0.5948

[1]p-value testing Treatment vs. Control obtained from Fisher's Exact Test.

At 6 months, the Treatment group had a significantly greater proportion of patients on nitrates (41.9%) compared to Control (23.2%). There was also a greater proportion of patients on hydralazine in the Treatment group (22.6%) compared to Control (15.0%). The proportion of subjects taking ACE-I/ARB's, B-blockers, aldosterone antagonists, and other diuretics was similar between the two (2) groups.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the heart failure cohort of 575 patients who underwent right heart catheterization (RHC). Of these 575 patients, 25 (4.3%) underwent a RHC, but did not receive an implant primarily because of anatomical/physiological conditions identified during the catheterization. The key safety outcomes for this study were evaluated at 6 months and are presented below in Table 12. Adverse effects are reported in Table 13.

a. Primary (Randomized Access (Part 1)) Safety Endpoint #1

This endpoint captured freedom from a DSRC through 6 months. It was tested against a pre-specified performance goal of 80%. The performance goal is similar to performance goals FDA has accepted for other permanent implants for heart failure devices. The analysis population included all subjects consented who had a right heart catheterization attempted.

There were 567 patients out of 575 patients that were free from DSRC. The freedom from DSRC rate was 98.6%, with a 95.2% lower confidence bound (LCB) of 97.3%. The pre-specified performance goal was 80%. The endpoint was met. These results are listed in Table 12 below.

Table 12. Primary Safety Endpoint #1- DSRC at 6 Months

Acute Safety Results	Sample Size (N=575)
Number of patients free from a DSRC	567 (98.6%)
95.2% Lower Confidence Boundry[1]	97.3%
p-value of H_0: Rate ≥80%	<0.0001[2]

[1]Exact 95.2% Clopper-Pearson lower confidence limit

[2]p-value from exact test of binomial proportions compared to 80% for all patients.

The adverse events included in the acute primary safety endpoint analysis are summarized in Table 13 below.

Table 13. Adverse Events in the Primary Safety Endpoint

Description	**Number of Subjects with Device or System related complication (%) (N = 575)**
Hemoptysis	1 (0.2%)
Sensor did not deploy	1 (0.2%)
Transient Ischemic Attack (TIA)	1 (0.2%)
Atypical chest pain	1 (0.2%)
Sepsis → death	1 (0.2%)
Atrial arrhythmia → death	1 (0.2%)
Arterial embolism (upper extremity)	1 (0.2%)
Pulmonary artery (in-situ) thrombus	1 (0.2%)
Total Subjects Experiencing a DSRC	**8 (1.4%[1], 95.2% LCB 97.3%)**

[1]DSRCs (8 total) by group: Consented by not randomized (2), Treatment (3), Control (3)

b. Primary (Randomized Access (Part 1)) Safety Endpoint #2

This endpoint captured the freedom from pressure sensor failure rate through 6 months. It was tested against a pre-specified performance goal of 90%. The analysis cohort included all subjects that had an investigational sensor implanted.

There were zero (0) pressure sensor failures out of 550 implanted devices. The freedom from pressure sensor failure rate was 100% with a 95.2% LCB of 99.3%. The pre-specified performance goal was 90%. This endpoint was met.

c. Open Access (Part 2) Safety Results

There were no Unanticipated Serious Adverse Device Events, Serious Adverse Device Events, Non-Serious Adverse Device Events, or Device-System Related Complications. In addition, there were no sensor failures over the entire study duration (mean follow-up of 26 months, range: 1 day – 44 months).

d. Adverse Events

Tables 14 through 17 identify the adverse events observed during both Part 1 and Part 2.

Table 14. Non-serious Adverse Events Not Related to the Device Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
All Patients with an Event	216 (80.0%)	1229	223 (79.6%)	1135	439 (79.8%)	2364	219 (63.1%)	787
Blood and lymphatic system disorders	27 (10.0%)	37	22 (7.9%)	28	49 (8.9%)	65	13 (3.7%)	16
Cardiac disorders	81 (30.0%)	140	69 (24.6%)	117	150 (27.3%)	257	49 (14.1%)	71
Congenital, familial and genetic disorders	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	3 (0.9%)	3
Ear and labyrinth disorders	6 (2.2%)	6	2 (0.7%)	2	8 (1.5%)	8	2 (0.6%)	2
Endocrine disorders	4 (1.5%)	4	9 (3.2%)	10	13 (2.4%)	14	7 (2.0%)	7
Eye disorders	12 (4.4%)	12	14 (5.0%)	16	26 (4.7%)	28	7 (2.0%)	8
Gastrointestinal disorders	64 (23.7%)	104	60 (21.4%)	96	124 (22.5%)	200	48 (13.8%)	70
General disorders and administration site conditions	64 (23.7%)	102	45 (16.1%)	80	109 (19.8%)	182	50 (14.4%)	62
Hepatobiliary disorders	1 (0.4%)	1	7 (2.5%)	10	8 (1.5%)	11	3 (0.9%)	3
Immune system disorders	4 (1.5%)	4	4 (1.4%)	4	8 (1.5%)	8	4 (1.2%)	4
Infections and infestations	76 (28.1%)	129	91 (32.5%)	150	167 (30.4%)	279	65 (18.7%)	99
Injury, poisoning and procedural complications	32 (11.9%)	44	32 (11.4%)	37	64 (11.6%)	81	32 (9.2%)	43
Investigations	32 (11.9%)	51	26 (9.3%)	40	58 (10.5%)	91	22 (6.3%)	25
Metabolism and nutrition disorders	66 (24.4%)	116	52 (18.6%)	88	118 (21.5%)	204	37 (10.7%)	53
Musculoskeletal and connective tissue disorders	49 (18.1%)	75	58 (20.7%)	73	107 (19.5%)	148	56 (16.1%)	70
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (2.2%)	8	9 (3.2%)	9	15 (2.7%)	17	6 (1.7%)	7

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Nervous system disorders	61 (22.6%)	86	50 (17.9%)	67	111 (20.2%)	153	47 (13.5%)	56
Psychiatric disorders	34 (12.6%)	46	29 (10.4%)	36	63 (11.5%)	82	25 (7.2%)	31
Renal and urinary disorders	33 (12.2%)	55	35 (12.5%)	45	68 (12.4%)	100	21 (6.1%)	21
Reproductive system and breast disorders	7 (2.6%)	8	16 (5.7%)	16	23 (4.2%)	24	11 (3.2%)	13
Respiratory, thoracic and mediastinal disorders	68 (25.2%)	97	70 (25.0%)	117	138 (25.1%)	214	47 (13.5%)	66
Skin and subcutaneous tissue disorders	23 (8.5%)	26	24 (8.6%)	28	47 (8.5%)	54	9 (2.6%)	9
Surgical and medical procedures	17 (6.3%)	21	16 (5.7%)	20	33 (6.0%)	41	16 (4.6%)	19
Vascular disorders	41 (15.2%)	57	39 (13.9%)	46	80 (14.5%)	103	27 (7.8%)	29

Table 15. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
All Patients with an Event	198 (73.3%)	797	217 (77.5%)	956	415 (75.5%)	1753	201 (57.9%)	647
Cardiac disorders	138 (51.1%)	333	151 (53.9%)	443	289 (52.5%)	776	119 (34.3%)	238
Congestive heart failure	99	204	121	274	220	478	80	140
Heart failure	10	15	13	22	23	37	10	12
Ventricular tachycardia*	10	14	12	16	22	30	8	9
Myocardial infarction*	7	7	14	14	21	21	9	9
Cardiac pain	13	19	7	22	20	41	0	0
Atrial fibrillation*	3	5	10	11	13	16	4	4
Cardiomyopathy	5	6	8	11	13	17	6	7
Cardiopulmonary arrest	3	3	7	7	10	10	3	3
Unstable angina	4	4	5	5	9	9	4	6
Coronary artery disease	5	5	3	3	8	8	4	4
Ventricular arrhythmia*	3	3	5	7	8	10	0	0
Ventricular fibrillation*	5	6	2	2	7	8	2	2
Anginal discomfort	1	1	5	8	6	9	2	4
Cardiac arrest	2	2	4	4	6	6	6	6
Ischemic cardiomyopathy	3	4	3	3	6	7	6	7
Atrial flutter*	2	2	3	3	5	5	3	3
Cardiogenic shock	2	2	3	3	5	5	3	3
Acute decompensated heart failure	2	2	1	1	3	3	0	0
ADHF	2	2	0	0	2	2	0	0
Acute coronary syndrome	1	2	1	1	2	3	1	1
Arrhythmia*	1	1	1	1	2	2	1	1
Atrial arrhythmia*	1	1	1	1	2	2	0	0
Cardiac failure	0	0	2	2	2	2	0	0
Heart disease, unspecified	1	1	1	1	2	2	1	1

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Non-ischemic cardiomyopathy	1	1	1	1	2	2	0	0
Sick sinus syndrome	1	1	1	1	2	2	0	0
Angina unstable	0	0	1	1	1	1	0	0
Arrhythmia ventricular*	1	1	0	0	1	1	0	0
Arrhythmia ventricular (NOS) *	1	1	0	0	1	1	0	0
Atrial tachycardia*	0	0	1	1	1	1	0	0
Bradycardia*	0	0	1	1	1	1	2	2
Bradycardia-tachycardia syndrome	0	0	1	1	1	1	0	0
Cardiac arrhythmia*	1	1	0	0	1	1	1	1
Cardiomegaly	0	0	1	1	1	1	0	0
Cardiorenal syndrome	1	1	0	0	1	1	1	2
Chronic heart failure	1	1	0	0	1	1	0	0
Congestive cardiac failure aggravated	0	0	1	1	1	1	0	0
Coronary artery disease progression	1	1	0	0	1	1	0	0
Coronary atherosclerosis	1	1	0	0	1	1	0	0
Coronary spasm	0	0	1	1	1	1	0	0
Decompensated heart failure	1	1	0	0	1	1	0	0
End stage cardiac failure	0	0	1	1	1	1	0	0
Heart failure, congestive	0	0	1	1	1	1	0	0
Heart valve incompetence	1	1	0	0	1	1	0	0
Intermediate coronary syndrome	0	0	1	1	1	1	0	0
Junctional tachycardia*	0	0	1	1	1	1	0	0
Left ventricular dysfunction	1	1	0	0	1	1	0	0
Mitral valve incompetence	1	1	0	0	1	1	1	1
Multi-valvular regurgitation	0	0	1	1	1	1	0	0

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Non ST segment elevation myocardial infarction*	1	1	0	0	1	1	0	0
Non-sustained ventricular tachycardia*	1	1	0	0	1	1	0	0
Pacemaker mediated tachycardia	1	1	0	0	1	1	0	0
Paroxysmal supraventricular tachycardia*	1	1	0	0	1	1	0	0
Pericardial disease	1	1	0	0	1	1	0	0
Pericardial effusion	1	1	0	0	1	1	0	0
Pericarditis	0	0	1	1	1	1	1	1
Premature ventricular contractions*	0	0	1	1	1	1	0	0
Supraventricular tachycardia*	0	0	1	1	1	1	0	0
Sustained ventricular tachycardia*	1	1	0	0	1	1	0	0
Tachycardia*	0	0	1	1	1	1	0	0
Tricuspid insufficiency	0	0	1	1	1	1	0	0
Ventricular ectopic beats	1	1	0	0	1	1	0	0
Ventricular rhythm*	0	0	1	1	1	1	0	0
Wide complex tachycardia	0	0	1	1	1	1	0	0
Wide complex ventricular tachycardia*	1	1	0	0	1	1	0	0
Asystole	0	0	0	0	0	0	2	2
Congestive cardiomyopathy	0	0	0	0	0	0	1	1
End stage heart disease	0	0	0	0	0	0	1	1
Hemopericardium	0	0	0	0	0	0	1	1
Palpitation	0	0	0	0	0	0	1	1
Paroxysmal atrial fibrillation	0	0	0	0	0	0	1	1
Polymorphic ventricular tachycardia	0	0	0	0	0	0	1	1

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Tachycardia supraventricular	0	0	0	0	0	0	1	1
Infections and infestations	45 (16.7%)	62	61 (21.8%)	90	106 (19.3%)	152	52 (15.0%)	76
Pneumonia	11	11	15	16	26	27	17	19
Urinary tract infection	5	7	5	6	10	13	5	5
Bronchitis	3	3	5	6	8	9	3	3
Cellulitis	1	1	6	7	7	8	1	1
Sepsis	3	4	4	4	7	8	7	9
Acute bronchitis	1	1	4	4	5	5	2	2
Bacteremia	1	1	3	5	4	6	2	2
Upper respiratory infection	2	2	2	2	4	4	1	1
Influenza	3	3	0	0	3	3	0	0
Cellulitis of leg	0	0	2	2	2	2	0	0
Cellulitis of legs	0	0	2	2	2	2	0	0
Central line infection	0	0	2	2	2	2	2	2
Endocarditis	0	0	2	2	2	2	0	0
Foot infection	2	3	0	0	2	3	0	0
Gastroenteritis	2	3	0	0	2	3	3	3
Incision site infection	1	3	1	4	2	7	1	1
Infection	0	0	2	2	2	2	1	1
Osteomyelitis	1	1	1	1	2	2	1	1
Pyelonephritis	1	1	1	1	2	2	0	0
Respiratory infection	1	1	1	1	2	2	0	0
Viral gastroenteritis	1	1	1	1	2	2	0	0
Abscess	1	1	0	0	1	1	0	0
Acute diverticulitis	1	1	0	0	1	1	0	0
Acute pyelonephritis	0	0	1	1	1	1	0	0
Bacterial endocarditis	0	0	1	1	1	1	0	0
Bacterial infection	1	1	0	0	1	1	0	0
C.difficile colitis	1	1	0	0	1	1	0	0

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Catheter site infection	0	0	1	1	1	1	0	0
Cellulitis of arm	0	0	1	1	1	1	0	0
Cellulitis of hand	1	1	0	0	1	1	0	0
Clostridium difficile infection	1	1	0	0	1	1	0	0
Community acquired pneumonia	0	0	1	1	1	1	1	1
Diverticulitis	1	1	0	0	1	1	2	2
Gastritis viral	0	0	1	1	1	1	0	0
Gastroenteritis adenovirus	1	1	0	0	1	1	0	0
Groin abscess	1	1	0	0	1	1	0	0
HIV-related dementia	0	0	1	1	1	1	0	0
Infection MRSA	0	0	1	1	1	1	0	0
Infection NOS	0	0	1	1	1	1	1	1
Klebsiella bacteremia	1	1	0	0	1	1	0	0
Maxillary sinusitis	1	1	0	0	1	1	0	0
Methicillin-resistant staphylococcal aureus sepsis	0	0	1	1	1	1	0	0
Obstructive pneumonia	1	1	0	0	1	1	0	0
Otitis media	0	0	1	1	1	1	0	0
Pneumonia MRSA	1	1	0	0	1	1	0	0
Prostatitis Escherichia coli	0	0	1	1	1	1	0	0
Purulent bronchitis	0	0	1	1	1	1	0	0
Salmonella infection, unspecified	0	0	1	1	1	1	0	0
Sepsis MRSA	0	0	1	1	1	1	1	2
Septic shock	0	0	1	1	1	1	3	3
Septicemia	0	0	1	1	1	1	0	0
Septicemia staphylococcal	0	0	1	1	1	1	0	0
Serratia infection	0	0	1	1	1	1	0	0
Sinusitis	0	0	1	1	1	1	1	1
Staphylococcal infection	1	1	0	0	1	1	0	0

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Urosepsis	1	1	0	0	1	1	0	0
Viral infection	1	1	0	0	1	1	1	1
Viremia	0	0	1	1	1	1	0	0
Wound infection	0	0	1	1	1	1	0	0
Arthritis infective	0	0	0	0	0	0	1	1
Bronchopneumonia	0	0	0	0	0	0	1	1
Clostridium difficile colitis	0	0	0	0	0	0	3	3
Cytomegalovirus viremia	0	0	0	0	0	0	1	1
Febrile cold (excl flu like illness)	0	0	0	0	0	0	1	1
Febrile infection	0	0	0	0	0	0	1	1
GI infection	0	0	0	0	0	0	1	1
Infection pseudomonas aeruginosa	0	0	0	0	0	0	1	1
MRSA colonization	0	0	0	0	0	0	1	1
MRSA wound infection	0	0	0	0	0	0	1	1
Pneumonia aspergillus	0	0	0	0	0	0	1	1
Septic joint	0	0	0	0	0	0	1	1
Suppurative peritonitis, other	0	0	0	0	0	0	1	1
Respiratory, thoracic and mediastinal disorders	44 (16.3%)	58	52 (18.6%)	85	96 (17.5%)	143	32 (9.2%)	40
Dyspnea	16	23	19	24	35	47	10	10
Respiratory failure	6	6	11	11	17	17	2	2
COPD exacerbation	4	4	11	20	15	24	5	5
Pleural effusion	3	3	3	4	6	7	3	3
Shortness of breath	4	4	2	3	6	7	0	0
Aspiration pneumonia	2	2	1	1	3	3	1	1
Epistaxis	0	0	3	3	3	3	2	2
Pulmonary hypertension	2	3	1	1	3	4	2	2
Respiratory distress	3	3	0	0	3	3	0	0
COPD	1	1	1	1	2	2	0	0
Dyspnea exertional	1	1	1	1	2	2	0	0

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Hypoxemia	0	0	2	2	2	2	0	0
Pneumonitis	0	0	2	2	2	2	0	0
Pulmonary edema	0	0	2	2	2	2	1	1
Pulmonary infiltration	0	0	2	2	2	2	1	1
Pulmonary thromboembolism	2	2	0	0	2	2	0	0
Acute respiratory failure	0	0	1	1	1	1	0	0
Apnea	1	1	0	0	1	1	0	0
Asthma	1	1	0	0	1	1	0	0
Asthma aggravated	0	0	1	1	1	1	0	0
Bronchitis asthmatic	0	0	1	1	1	1	0	0
Difficulty breathing	0	0	1	1	1	1	0	0
Dyspnea exacerbated	1	1	0	0	1	1	0	0
Exacerbation of asthma	0	0	1	1	1	1	0	0
Hemoptysis	0	0	1	1	1	1	1	3
Hypoxia	0	0	1	1	1	1	3	3
Productive cough	0	0	1	1	1	1	0	0
Pulmonary mass	1	1	0	0	1	1	0	0
Respiratory arrest	1	2	0	0	1	2	0	0
Chronic obstructive pulmonary disease	0	0	0	0	0	0	3	3
Cough	0	0	0	0	0	0	1	1
Hypoventilation	0	0	0	0	0	0	1	1
Pulmonary embolus	0	0	0	0	0	0	1	1
Tachypnea	0	0	0	0	0	0	1	1
General disorders and administration site conditions	35 (13.0%)	43	30 (10.7%)	40	65 (11.8%)	83	36 (10.4%)	46
Chest pain	16	20	10	11	26	31	17	26
Weakness	3	5	7	7	10	12	0	0
Chest pain (non-cardiac)	2	2	4	7	6	9	0	0
Fever	1	1	3	3	4	4	2	2
General malaise	3	3	0	0	3	3	1	1

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Death	1	1	1	1	2	2	7	7
Pain	2	2	0	0	2	2	0	0
Sudden cardiac death	1	1	1	1	2	2	1	1
Anasarca	0	0	1	1	1	1	0	0
Central line complication	1	2	0	0	1	2	0	0
Chest discomfort	0	0	1	1	1	1	0	0
Chest pain aggravated	0	0	1	1	1	1	0	0
Chronic fatigue	0	0	1	1	1	1	0	0
Edema of lower extremities	1	2	0	0	1	2	2	2
Fatigue	1	1	0	0	1	1	0	0
Fatigue extreme	1	1	0	0	1	1	0	0
Febrile reaction	0	0	1	1	1	1	0	0
Fever of unknown origin	0	0	1	1	1	1	1	1
Infusion site bleeding	0	0	1	1	1	1	0	0
Multi-organ failure	0	0	1	1	1	1	0	0
Non-cardiac chest pain	0	0	1	1	1	1	1	1
Substernal chest pain	0	0	1	1	1	1	0	0
Sudden death	1	1	0	0	1	1	0	0
Swelling	1	1	0	0	1	1	0	0
Edema	0	0	0	0	0	0	1	1
Malaise	0	0	0	0	0	0	1	1
Organ failure	0	0	0	0	0	0	1	1
Thrombus in catheter	0	0	0	0	0	0	1	1
Ulcer	0	0	0	0	0	0	1	1
Vascular disorders	33 (12.2%)	42	27 (9.6%)	28	60 (10.9%)	70	15 (4.3%)	15
Hypotension	15	20	13	14	28	34	6	6
Hematoma	2	2	2	2	4	4	0	0
Orthostatic hypotension	2	2	2	2	4	4	0	0
Deep vein thrombosis leg	3	4	0	0	3	4	0	0
Low output state	3	3	0	0	3	3	0	0

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Peripheral arterial disease	2	2	1	1	3	3	0	0
Claudication	2	2	0	0	2	2	1	1
DVT of legs	2	2	0	0	2	2	0	0
Aortic stenosis	0	0	1	1	1	1	0	0
Arterial thrombosis (limbs)	1	1	0	0	1	1	0	0
DVT	0	0	1	1	1	1	1	1
Deep vein thrombosis	0	0	1	1	1	1	0	0
Extremity necrosis	0	0	1	1	1	1	0	0
Hemorrhage, unspecified	1	1	0	0	1	1	0	0
Hemorrhagic shock	1	1	0	0	1	1	0	0
Hypertension	0	0	1	1	1	1	1	1
Hypovolemic shock	1	1	0	0	1	1	2	2
Labile blood pressure	0	0	1	1	1	1	0	0
Peripheral vascular disease	0	0	1	1	1	1	0	0
Shock hemorrhagic	0	0	1	1	1	1	0	0
Subclavian artery thrombosis	1	1	0	0	1	1	0	0
Thromboembolic event	0	0	1	1	1	1	0	0
Bleeding	0	0	0	0	0	0	1	1
Cardiovascular collapse	0	0	0	0	0	0	1	1
Hypertensive emergency	0	0	0	0	0	0	1	1
Ischemia	0	0	0	0	0	0	1	1
Nervous system disorders	29 (10.7%)	37	28 (10.0%)	38	57 (10.4%)	75	27 (7.8%)	32
Syncope	12	15	7	8	19	23	9	13
CVA	2	2	4	4	6	6	2	2
Stroke	3	3	2	2	5	5	3	3
Presyncope	0	0	3	3	3	3	2	2
Carotid artery stenosis	1	1	1	1	2	2	0	0
Dizziness	1	1	1	1	2	2	1	1
Embolic stroke	1	1	1	1	2	2	0	0

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Subarachnoid hemorrhage	1	1	1	1	2	2	0	0
Anoxic encephalopathy	0	0	1	1	1	1	0	0
Ataxia	1	1	0	0	1	1	0	0
Cerebellar infarction	1	1	0	0	1	1	0	0
Cerebral degeneration	1	1	0	0	1	1	0	0
Cerebral infarct	0	0	1	1	1	1	0	0
Cerebrovascular accident	1	1	0	0	1	1	0	0
Disorder brain (chronic)	1	1	0	0	1	1	0	0
Embolic cerebral infarction	0	0	1	1	1	1	0	0
Encephalopathy	0	0	1	1	1	1	1	1
Headache	0	0	1	1	1	1	0	0
Hemorrhagic stroke	0	0	1	1	1	1	0	0
Hepatic encephalopathy	1	1	0	0	1	1	0	0
Hypertensive encephalopathy	0	0	1	1	1	1	0	0
Intracranial hemorrhage	1	1	0	0	1	1	0	0
Ischemic stroke	0	0	1	1	1	1	0	0
Loss of consciousness	1	2	0	0	1	2	1	1
Numbness	0	0	1	2	1	2	0	0
Ophthalmoplegic migraine	0	0	1	1	1	1	0	0
Paresthesia	0	0	1	1	1	1	0	0
Sciatica	1	1	0	0	1	1	0	0
Seizure	1	1	0	0	1	1	0	0
Slurred speech	0	0	1	1	1	1	0	0
Somnolence	1	1	0	0	1	1	0	0
Syncope convulsive	1	1	0	0	1	1	0	0
TIA	0	0	1	1	1	1	2	2
Unresponsive to stimuli	0	0	1	1	1	1	1	1
Vasovagal symptoms	0	0	1	1	1	1	0	0
Weakness left or right side	0	0	1	1	1	1	0	0
Brain injury	0	0	0	0	0	0	1	1

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Restless leg syndrome	0	0	0	0	0	0	1	1
Todd's paralysis	0	0	0	0	0	0	1	1
Transient ischemic attacks	0	0	0	0	0	0	2	2
Vocal cord paralysis	0	0	0	0	0	0	1	1
Renal and urinary disorders	33 (12.2%)	41	24 (8.6%)	34	57 (10.4%)	75	20 (5.8%)	22
Acute on chronic renal failure	11	12	9	10	20	22	1	1
Acute renal failure	9	10	7	9	16	19	8	9
Renal insufficiency	9	11	3	4	12	15	5	5
Acute renal insufficiency	0	0	2	2	2	2	0	0
Azotemia	1	1	1	1	2	2	0	0
Chronic kidney disease	1	1	1	1	2	2	0	0
Renal failure	1	1	1	1	2	2	1	1
Acute tubular necrosis	0	0	1	1	1	1	0	0
Chronic renal failure worsened	0	0	1	1	1	1	0	0
End stage renal failure	0	0	1	1	1	1	0	0
Hematuria	1	1	0	0	1	1	0	0
Kidney failure	1	1	0	0	1	1	0	0
Lupus nephritis	0	0	1	1	1	1	0	0
Nephrolithiasis	1	1	0	0	1	1	0	0
Renal artery stenosis	1	1	0	0	1	1	0	0
Renal function abnormal	1	1	0	0	1	1	0	0
Uremia	0	0	1	1	1	1	0	0
Urinary retention	0	0	1	1	1	1	2	2
Chronic renal failure	0	0	0	0	0	0	1	1
Kidney disorder	0	0	0	0	0	0	1	1
Renal disease	0	0	0	0	0	0	1	1
Renal failure acute on chronic	0	0	0	0	0	0	1	1
Gastrointestinal disorders	24 (8.9%)	35	31 (11.1%)	49	55 (10.0%)	84	36 (10.4%)	53

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
GI bleed	6	7	7	7	13	14	9	10
Abdominal pain	3	3	5	6	8	9	2	2
Diarrhea	4	4	1	1	5	5	2	2
Nausea	4	4	1	1	5	5	0	0
Gastritis	3	3	1	1	4	4	1	1
Gastrointestinal bleed	0	0	4	6	4	6	6	8
Vomiting	2	2	2	4	4	6	1	1
Constipation	0	0	3	3	3	3	1	1
Pancreatitis	2	2	1	1	3	3	1	1
Ascites	2	2	0	0	2	2	0	0
Dysphagia	1	1	1	1	2	2	2	2
Emesis	2	2	0	0	2	2	0	0
Esophagitis	0	0	2	2	2	2	0	0
Gastroparesis	0	0	2	2	2	2	1	2
Abdominal bloating	1	1	0	0	1	1	0	0
Abdominal wall hematoma	0	0	1	1	1	1	0	0
Chronic epigastric pain	0	0	1	1	1	1	0	0
Dental caries	0	0	1	1	1	1	0	0
Esophageal spasm	1	1	0	0	1	1	0	0
Esophagitis ulcerative	1	1	0	0	1	1	0	0
Gastric polyps	0	0	1	1	1	1	0	0
Gastritis erosive	0	0	1	1	1	1	0	0
Ileus	0	0	1	1	1	1	0	0
Incarcerated umbilical hernia	0	0	1	1	1	1	0	0
Ischemic colitis	0	0	1	1	1	1	1	2
Melena	1	1	0	0	1	1	0	0
Odynophagia	0	0	1	1	1	1	0	0
Rectal bleeding	0	0	1	3	1	3	1	1
Rectal fistula	0	0	1	1	1	1	0	0
Rectal prolapse	0	0	1	1	1	1	0	0

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Ventral hernia	1	1	0	0	1	1	2	4
Decay dental	0	0	0	0	0	0	1	1
Duodenitis	0	0	0	0	0	0	1	1
Fecal impaction (causing obstruction)	0	0	0	0	0	0	1	1
Gastric ulcer	0	0	0	0	0	0	1	1
Gastric ulcer haemorrhage	0	0	0	0	0	0	1	1
Gastro intestinal bleed	0	0	0	0	0	0	1	1
Gastrointestinal bleeding	0	0	0	0	0	0	2	2
Hematemesis	0	0	0	0	0	0	1	2
Hematochezia	0	0	0	0	0	0	2	2
Mesenteric ischemia	0	0	0	0	0	0	1	1
Reflux esophagitis	0	0	0	0	0	0	1	1
Right upper quadrant pain	0	0	0	0	0	0	1	1
Small bowel obstruction	0	0	0	0	0	0	1	1
Metabolism and nutrition disorders	26 (9.6%)	33	28 (10.0%)	38	54 (9.8%)	71	24 (6.9%)	30
Dehydration	7	9	5	5	12	14	8	8
Hyperglycemia	3	4	5	6	8	10	1	1
Hypoglycemia	4	4	2	2	6	6	2	2
Failure to thrive	2	2	3	4	5	6	1	1
Hypokalemia	2	2	3	3	5	5	3	3
Hypovolemia	2	2	3	3	5	5	0	0
Electrolyte imbalance	2	2	2	2	4	4	0	0
Hypervolemia	2	2	2	2	4	4	0	0
Hyponatremia	1	1	3	3	4	4	4	4
Diabetes	2	2	1	1	3	3	0	0
Hyperkalemia	1	1	2	2	3	3	1	1
Diabetes mellitus loss of control	1	1	1	1	2	2	0	0
Anorexia	0	0	1	1	1	1	0	0
Diabetes mellitus	1	1	0	0	1	1	0	0

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Hypercalcemia	0	0	1	1	1	1	0	0
Ketoacidosis (diabetic)	0	0	1	1	1	1	0	0
Volume overload	0	0	1	1	1	1	0	0
Diabetes mellitus inadequate control	0	0	0	0	0	0	1	1
Diabetic ketoacidosis	0	0	0	0	0	0	1	1
Gout	0	0	0	0	0	0	1	1
Gout aggravated	0	0	0	0	0	0	2	2
Gout flare	0	0	0	0	0	0	2	3
Hyperosmolar state	0	0	0	0	0	0	1	1
Hypoglycemic attack	0	0	0	0	0	0	1	1
Surgical and medical procedures	24 (8.9%)	28	29 (10.4%)	34	53 (9.6%)	62	14 (4.0%)	15
Implantable cardioverter defibrillator insertion	4	4	2	2	6	6	0	0
Pacemaker battery replacement	1	1	5	5	6	6	3	3
Cardiac resynchronisation therapy	2	2	2	2	4	4	0	0
Heart transplant	1	1	3	3	4	4	2	2
Cardiac catheterization	3	5	0	0	3	5	0	0
Implantable defibrillator replacement	0	0	3	3	3	3	0	0
Amputation	0	0	2	2	2	2	0	0
Cardiac ablation	1	1	1	1	2	2	0	0
Cardiac resynchronization therapy	0	0	2	2	2	2	0	0
Cardioversion	1	1	1	1	2	2	0	0
Cholecystectomy	0	0	2	2	2	2	0	0
Foot surgery	1	1	1	1	2	2	1	1
Inguinal hernia repair	1	1	1	1	2	2	0	0
Abdominal hernia repair	1	1	0	0	1	1	0	0
Brachytherapy	1	1	0	0	1	1	0	0

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Cardiac pacemaker revision	1	1	0	0	1	1	0	0
Central line placement	0	0	1	1	1	1	0	0
Colostomy closure	1	1	0	0	1	1	0	0
Epicardial lead placement	1	1	0	0	1	1	1	1
Gallbladder operation	0	0	1	1	1	1	0	0
Gastric bypass	0	0	1	1	1	1	0	0
Implantable defibrillator insertion	1	1	0	0	1	1	1	1
Incisional drainage	1	1	0	0	1	1	0	0
Knee total replacement	0	0	1	1	1	1	0	0
Mitral valve replacement	0	0	1	1	1	1	0	0
Neuroma removal	1	1	0	0	1	1	0	0
Parotidectomy	0	0	1	1	1	1	0	0
Polypectomy	1	1	0	0	1	1	0	0
Stent placement	1	1	0	0	1	1	0	0
Total hip replacement	1	1	0	0	1	1	0	0
Total knee replacement	0	0	1	2	1	2	0	0
Tricuspid valve repair	0	0	1	1	1	1	0	0
Arteriovenous graft	0	0	0	0	0	0	1	1
Catheterization cardiac	0	0	0	0	0	0	2	2
Hospitalization NOS	0	0	0	0	0	0	1	1
Knee surgery NOS	0	0	0	0	0	0	1	1
Left ventricular assist device insertion	0	0	0	0	0	0	1	1
Ventricular assist device insertion	0	0	0	0	0	0	1	1
Injury, poisoning and procedural complications	18 (6.7%)	21	16 (5.7%)	19	34 (6.2%)	40	15 (4.3%)	16
Lead dislodgement	2	2	2	2	4	4	0	0
Hip fracture	0	0	3	3	3	3	1	1
Bleeding postoperative	1	1	1	1	2	2	0	0
Device malfunction	0	0	2	2	2	2	0	0

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Fall	2	2	0	0	2	2	2	2
Head injury	0	0	2	2	2	2	0	0
Lead conductor fracture	2	2	0	0	2	2	0	0
Subdural hematoma	2	2	0	0	2	2	2	2
Accidental overdose	1	1	0	0	1	1	0	0
Ankle fracture	1	1	0	0	1	1	0	0
Cardiac pacemaker malfunction	0	0	1	1	1	1	0	0
Compression fracture	0	0	1	1	1	1	0	0
Contusion	0	0	1	1	1	1	0	0
Device lead damage	0	0	1	1	1	1	0	0
Device lead issue	1	1	0	0	1	1	0	0
Digoxin toxicity	1	1	0	0	1	1	3	3
Femur fracture	0	0	1	1	1	1	0	0
Fracture rib	1	1	0	0	1	1	0	0
Fractured hip	1	1	0	0	1	1	0	0
Fractured nose	1	1	0	0	1	1	0	0
Fractured pelvis NOS	1	1	0	0	1	1	0	0
Hematoma traumatic	1	1	0	0	1	1	0	0
Humerus fracture	0	0	1	1	1	1	0	0
Medical device complication	0	0	1	1	1	1	0	0
Migration of implant	1	1	0	0	1	1	0	0
Motor vehicle accident	1	1	0	0	1	1	0	0
Pneumothorax traumatic	1	1	0	0	1	1	0	0
Skin avulsion injury	0	0	1	1	1	1	0	0
Subdural haemorrhage	0	0	1	1	1	1	0	0
Chemical pneumonitis	0	0	0	0	0	0	1	1
Device complication	0	0	0	0	0	0	5	5
Overdose accidental	0	0	0	0	0	0	1	1
Sciatic nerve injury	0	0	0	0	0	0	1	1

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Musculoskeletal and connective tissue disorders	11 (4.1%)	14	13 (4.6%)	13	24 (4.4%)	27	16 (4.6%)	17
Back pain	0	0	2	2	2	2	1	1
Chest wall pain	1	1	1	1	2	2	0	0
Degenerative joint disease	1	1	1	1	2	2	1	1
Arthritis	1	1	0	0	1	1	1	1
Arthritis single joint	0	0	1	1	1	1	0	0
Back pain aggravated	1	2	0	0	1	2	0	0
Charcot's joint	0	0	1	1	1	1	0	0
Groin pain	0	0	1	1	1	1	0	0
Hemarthrosis involving lower leg	1	1	0	0	1	1	0	0
Lumbar spinal stenosis	0	0	1	1	1	1	0	0
Lupus erythematosus	0	0	1	1	1	1	1	2
Muscle necrosis	1	1	0	0	1	1	0	0
Musculoskeletal chest pain	1	1	0	0	1	1	0	0
Neck pain	1	1	0	0	1	1	1	1
Olecranon bursitis	0	0	1	1	1	1	0	0
Osteoarthritis knee	0	0	1	1	1	1	0	0
Polymyositis	1	1	0	0	1	1	0	0
Pseudogout	0	0	1	1	1	1	0	0
Rheumatoid arthritis	1	1	0	0	1	1	0	0
Rotator cuff tear	1	1	0	0	1	1	1	1
Scleroderma	0	0	1	1	1	1	0	0
Shoulder blade pain	1	1	0	0	1	1	0	0
Spinal column stenosis	1	1	0	0	1	1	0	0
Cervical spondylosis	0	0	0	0	0	0	1	1
Foot pain	0	0	0	0	0	0	1	1
Joint instability	0	0	0	0	0	0	1	1
Knee pain	0	0	0	0	0	0	1	1
Low back pain	0	0	0	0	0	0	1	1

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Osteoarthritis knees	0	0	0	0	0	0	1	1
Pain in joint involving lower leg	0	0	0	0	0	0	1	1
Shoulder pain	0	0	0	0	0	0	1	1
Spinal stenosis NOS	0	0	0	0	0	0	1	1
Spondylolisthesis	0	0	0	0	0	0	1	1
Blood and lymphatic system disorders	13 (4.8%)	14	10 (3.6%)	13	23 (4.2%)	27	14 (4.0%)	20
Anemia	11	12	8	10	19	22	11	12
Thrombocytopenia	1	1	1	1	2	2	1	1
Anemia microcytic	1	1	0	0	1	1	0	0
Leukocytosis	0	0	1	1	1	1	0	0
Neutropenia	0	0	1	1	1	1	0	0
Anemia aggravated	0	0	0	0	0	0	1	1
Hemolysis	0	0	0	0	0	0	1	5
Neutropenic fever	0	0	0	0	0	0	1	1
Investigations	10 (3.7%)	10	5 (1.8%)	6	15 (2.7%)	16	3 (0.9%)	4
Serum creatinine increased	2	2	1	2	3	4	0	0
Transplant evaluation	2	2	0	0	2	2	0	0
Anticoagulation drug level above therapeutic	1	1	0	0	1	1	0	0
Blood culture positive	1	1	0	0	1	1	0	0
Blood glucose fluctuation	0	0	1	1	1	1	0	0
INR	0	0	1	1	1	1	0	0
INR increased	1	1	0	0	1	1	0	0
International normalized ratio decreased	0	0	1	1	1	1	0	0
Mediastinoscopy	1	1	0	0	1	1	0	0
Pulmonary arterial pressure increased	1	1	0	0	1	1	1	1
QT interval prolonged	1	1	0	0	1	1	0	0

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Ventricular filling pressure increased	0	0	1	1	1	1	0	0
Blood sugar abnormal	0	0	0	0	0	0	1	1
INR decreased	0	0	0	0	0	0	1	1
Urinary output diminished	0	0	0	0	0	0	1	1
Psychiatric disorders	7 (2.6%)	7	7 (2.5%)	7	14 (2.5%)	14	6 (1.7%)	7
Acute mental status changes	3	3	7	7	10	10	4	4
Agitation	1	1	0	0	1	1	0	0
Delirium toxic	1	1	0	0	1	1	0	0
Panic attack	1	1	0	0	1	1	0	0
Suicidal ideation	1	1	0	0	1	1	0	0
Mental status changes	0	0	0	0	0	0	2	2
Withdrawal syndrome	0	0	0	0	0	0	1	1
Hepatobiliary disorders	6 (2.2%)	8	7 (2.5%)	8	13 (2.4%)	16	2 (0.6%)	3
Acute cholecystitis	4	4	0	0	4	4	0	0
Cholecystitis	1	1	3	3	4	4	0	0
Cholelithiasis	2	2	0	0	2	2	2	2
Gallstones	0	0	1	1	1	1	1	1
Hepatic fibrosis	0	0	1	2	1	2	0	0
Injury to liver	1	1	0	0	1	1	0	0
Liver disorder	0	0	1	1	1	1	0	0
Portal hypertension	0	0	1	1	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (1.9%)	7	4 (1.4%)	5	9 (1.6%)	12	5 (1.4%)	5
Lung cancer	2	2	1	1	3	3	1	1
Large cell lung cancer	0	0	1	1	1	1	0	0
Lung nodule	0	0	1	1	1	1	0	0
Lymphocytic leukemia	0	0	1	1	1	1	0	0
Myelodysplastic syndrome	1	1	0	0	1	1	0	0

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Ovarian cancer	1	1	0	0	1	1	0	0
Prostate cancer metastatic	0	0	1	1	1	1	0	0
Skin cancer	1	1	0	0	1	1	0	0
Small cell carcinoma of the lung	1	2	0	0	1	2	0	0
Adenoma	0	0	0	0	0	0	1	1
Breast cancer	0	0	0	0	0	0	1	1
Esophageal cancer	0	0	0	0	0	0	1	1
Lymphoma	0	0	0	0	0	0	1	1
Endocrine disorders	2 (0.7%)	2	1 (0.4%)	1	3 (0.5%)	3	1 (0.3%)	1
Adrenal insufficiency	1	1	0	0	1	1	0	0
Hypothyroidism	1	1	0	0	1	1	1	1
Myxedema	0	0	1	1	1	1	0	0
Immune system disorders	2 (0.7%)	2	1 (0.4%)	1	3 (0.5%)	3	0 (0.0%)	0
Amyloidosis	1	1	0	0	1	1	0	0
Heart transplant rejection	0	0	1	1	1	1	0	0
Transplant rejection	1	1	0	0	1	1	0	0
Skin and subcutaneous tissue disorders	0 (0.0%)	0	3 (1.1%)	3	3 (0.5%)	3	3 (0.9%)	4
Diabetic ulcer	0	0	1	1	1	1	0	0
Foot ulcer	0	0	1	1	1	1	0	0
Venous stasis ulcer	0	0	1	1	1	1	0	0
Decubitus ulcer	0	0	0	0	0	0	1	1
Rash	0	0	0	0	0	0	1	2
Skin thinning of	0	0	0	0	0	0	1	1
Benign prostatic hypertrophy	0	0	1	1	1	1	0	0
Reproductive system and breast disorders	0 (0.0%)	0	1 (0.4%)	1	1 (0.2%)	1	3 (0.9%)	3
Enlarged prostate	0	0	0	0	0	0	1	1
Postmenopausal bleeding	0	0	0	0	0	0	1	1
Vaginal bleeding	0	0	0	0	0	0	1	1

Table 16. Adverse Device Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subject	Events	Subject	Events
Unanticipated Serious Adverse Device Events	0 (0.0%)	0	1 (0.4%)	1	1 (0.2%)	1	0 (0.0%)	0
Serious Adverse Device Events	2 (0.7%)	2	0 (0.0%)	0	2 (0.4%)	2	0 (0.0%)	0

i. Unanticipated Serious Adverse Device Events (USADE)

There was one (1) event during Part 1 reported as a USADE by the investigator (one (1) subject reported feeling a "shock" from the home unit). The event was determined not to be serious or device/system related by the Clinical Events Committee (CEC). There were no additional USADEs during the remainder of Part 1 or during Part 2 of the clinical trial.

ii. Serious Adverse Device Events (SADEs)

The two (2) SADEs that occurred during Part 1 were hemoptysis during the implant procedure and an in-situ thrombosis during the right heart catheterization procedure. Both patients were treated and recovered without sequela. There were no additional SADEs during the remainder of Part 1 or over Part 2 of the clinical trial.

iii. Non-Serious Adverse Device Events

There were 17 non-serious adverse device events that occurred over Part 1. There were no additional non-serious adverse device events during the remainder of Part 1 or over Part 2 of the clinical trial. These events were rare and are well known adverse events that occur during right heart catheterization procedures.

Table 17. Non-serious Adverse Device Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
All Patients with an Event	5 (1.9%)	6	7 (2.5%)	11	12 (2.2%)	17	0 (0%)	0
General disorders and administration site conditions	1 (0.4%)	1	4 (1.4%)	6	5 (0.9%)	7	0 (0%)	0
Investigations	2 (0.7%)	2	1 (0.4%)	1	3 (0.5%)	3	0 (0%)	0
Respiratory, thoracic and mediastinal disorders	2 (0.7%)	2	1 (0.4%)	1	3 (0.5%)	3	0 (0%)	0
Cardiac disorders	1 (0.4%)	1	1 (0.4%)	1	2 (0.4%)	2	0 (0%)	0
Nervous system disorders	0 (0.0%)	0	1 (0.4%)	1	1 (0.2%)	1	0 (0%)	0
Vascular disorders	0 (0.0%)	0	1 (0.4%)	1	1 (0.2%)	1	0 (0%)	0

2. Randomized Access (Part 1) Effectiveness Endpoints

The analysis of effectiveness was based on the 550 patients receiving a sensor implant. Primary effectiveness outcomes were evaluated at 6 months and are presented in Table 18.

The analysis of the primary effectiveness endpoint was confounded by study conduct, specifically patient-specific management recommendations contained in nurse communications to the study investigators. Details of these analyses are nonetheless included below.

a. Primary Effectiveness Endpoint

This endpoint captured the rate of heart failure related (HFR) hospitalizations through 6 months. Hospitalization events were reviewed by the Clinical Events Committee (CEC) and adjudicated in terms of heart failure related vs. not related.

In the Treatment group, 55 subjects experienced a total of 84 hospitalizations (out of a total of 270 patients), resulting in an HFR hospitalization rate of 0.32 events/patient/6 months.

In the Control group, 80 patients experienced a total of 120 HFR hospitalizations (out of total of 280 patients), resulting in an HFR hospitalization rate of 0.44 events/patient/6 months.

This difference between the groups represented a 28% reduction in the 6-month rate of HF hospitalization in the Treatment group. Using the negative binomial regression model, the p-value was 0.0002. Due to an interim

analysis (and corresponding alpha spending), the result was tested at a significance level of 0.048. The endpoint was met.

Table 18. Primary Effectiveness Endpoint – Heart Failure Related Hospitalizations

	Treatment (270)		Control (280)		All Patients (550)
	# Hosp.	Hosp. Rate (events/ patient-6 mos.)	# Hosp.	Hosp. Rate (events/ patient-6 mos.)	NBR p-value[1]
Up to 6 Months	84	0.32	120	0.44	0.0002

[1]P-value from the test for $\beta_1 = 0$ in the negative binomial regression (NBR) model.

b. Secondary Effectiveness Endpoints

i. Change From Baseline to 6 Months in PA Mean Pressures

The change in pressure over the first 6 months was evaluated by integrating the area under the pressure curve (AUC). The patient's baseline pressures (first seven (7) days of home readings) were used to calculate an average pressure, which was then used as the "baseline" for the remainder of the first 6 months. Subsequent pressure readings were then compared to this "baseline," with readings above the baseline considered "positive" and readings below the baseline considered "negative." A positive AUC indicates PA mean pressures were higher than the baseline and a negative AUC indicates PA mean pressures were lower than the baseline.

As seen in Table 19 and Figure 7 below, the Treatment and Control patients had similar baseline PA pressures. Over 6 months of follow-up, the Treatment group had a reduction in AUC mean pressures of -155.7 mmHg days, compared to the Control group which had an increase in AUC mean pressures of 33.1 mmHg days. The reported p-value for this comparison was 0.0077; secondary endpoint #1 was met. This result strongly suggests that use of the CardioMEMS HF System is associated with a significantly greater decrease in PA Pressures than was observed for the Control group.

Table 19. Secondary Effectiveness Endpoint - Change From Baseline in PA Mean Pressures

	Treatment (270)	Control (280)	All Patients (550)	p-value
Baseline Reference[3]				
Mean±StdDev (mmHg) (N)	31.3±11.1 (265)	31.8±10.7 (272)	31.6±10.9 (537)	0.5562[1]
Median	30.1	31.0	30.8	
(Min, Max)	(2.0, 61.6)	(3.7, 60.4)	(2.0, 61.6)	
Change from Baseline (AUC)[4]				
Mean±StdDev (mmHg days) (N)	-155.7±1088.0 (265)	33.1±951.7 (272)	-60.1±1024.6 (537)	0.0077[2]
Median (H-L estimate)[5]	-7.2 (-115.6)	33.7 (47.4)	19.5 (-19.3)	
(Min, Max)	(-3121.1, 4782.5)	(-3694.0, 5725.7)	(-3694.0, 5725.7)	

[1]P-value from two-group t-test

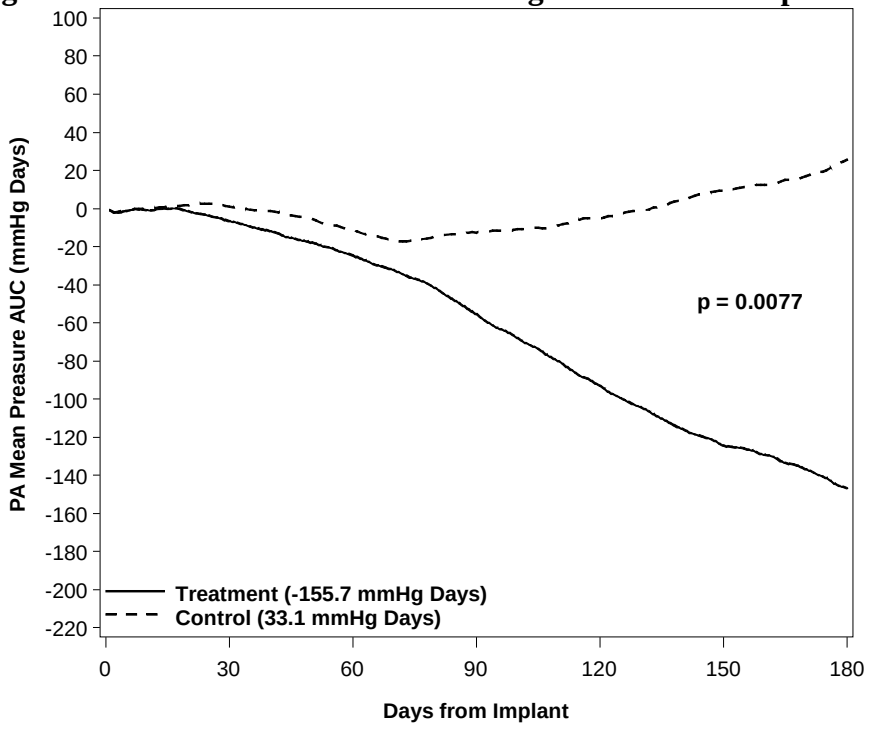
[2]P-value from analysis of covariance with baseline pressure as the covariate

[3]Baseline represents the average of the first 7 days of pressure readings taken from home

[4]AUC = integration of area under the curve of all pressure readings up to 6 months using baseline pressure as the reference point. Positive values represent area values above the Baseline and negative values represent area values below the Baseline.

[5]Due to skewness in the data, both centrally and in the tails, the Hodges-Lehmann estimate (Hodges & Lehmann, 1983) is also presented as an estimator of central tendency.

Figure 7. AUC PA Mean Pressure Change from Baseline up to 6 Months



ii. Proportion of Patients Hospitalized for Heart Failure

In contrast to the primary effectiveness endpoint, which assessed the rate of HFR hospitalization, this secondary endpoint assessed the proportion of subjects hospitalized for heart failure. See Table 20 below.

During the 6 month follow up period, 55 (20.4%) out of 270 Treatment and 80 (28.6%) out of 280 Control patients suffered a HFR hospitalization (p=0.0292). Secondary endpoint #2 was met.

Table 20. Proportion of Subjects Hospitalized for Heart Failure

	Treatment (270)	Control (280)	All Patients (550)	p-value[1]
Subjects Hospitalized for Heart Failure				
Hospitalized	55 (20.4%)	80 (28.6%)	135 (24.5%)	0.0292
Not Hospitalized	215 (79.6%)	200 (71.4%)	415 (75.5%)	

[1] P-value from Fisher's exact test

iii. Days Alive Outside of the Hospital

Days alive outside of the hospital were defined as days without a HFR hospitalization. At 6 months, for the Treatment group the average number of days alive outside of the hospital was 174.4 ± 31.1 compared to the Control group average of 172.1 ± 37.8. The reported p-value for this endpoint was 0.0280. See Table 21 below.

The average number of days hospitalized was 2.2 ± 6.8 days in the Treatment group compared to 3.8 ± 11.1 days in the Control group. Secondary endpoint #3 was met.

Table 21. Days Alive Outside of the Hospital

	Treatment (270)	Control (280)	All Patients (550)	p-value
Total Days Alive				
Mean±StdDev (N)	176.6±29.6 (270)	175.9±35.4 (280)	176.3±32.6 (550)	0.4451[1]
Median	180.0	180.0	180.0	
(Min, Max)[3]	(4.0, 281.0)	(1.0, 300.0)	(1.0, 300.0)	
Sum	47,686	49,259	96,945	
Days Alive Outside Hospital				
Mean±StdDev (N)	174.4±31.1 (270)	172.1±37.8 (280)	173.3±34.7 (550)	0.0280[2]
Median	179.0	178.0	179.0	
(Min, Max)[3]	(4.0, 281.0)	(1.0, 300.0)	(1.0, 300.0)	
Sum	47,097	48,201	95,298	
Days Hospitalized				
Mean±StdDev (N)	2.2±6.8 (270)	3.8±11.1 (280)	3.0±9.3 (550)	0.0246[1]
Median	0.0	0.0	0.0	
(Min, Max)	(0.0, 66.0)	(0.0, 88.0)	(0.0, 88.0)	
Sum	589	1,058	1,647	

[1]P-value from Wilcoxon Rank Sum test

[2]P-value from Wilcoxon Rank Sum test after controlling for patient duration in study (i.e., Days Alive Outside Hospital / Patient Duration x 180)

[3]A few patients had 6 month visit deviations which account for the large number of follow-up days

iv. Quality of Life – Minnesota Living with Heart Failure Questionnaire (MLHFQ)

Heart failure specific quality of life was assessed with the MLHFQ total score at 6 months. At 6 months, the average total score in the Treatment group was 45.2 ± 26.4; the average total score in the Control group 50.6 ± 24.8. Using a two-group t-test, the p value was 0.0236. Secondary endpoint #4 was met. See Table 22 below.

Table 22. Quality of Life – MLHFQ

	Treatment (270)	Control (280)	All Patients (550)	p-value[1]
6 Month Follow-up – Total Score				
Mean±StdDev (N)	45.2±26.4 (229)	50.6±24.8 (236)	48.0±25.7 (465)	0.0236
Median	45.0	52.0	49.0	
(Min, Max)	(0.0, 100.0)	(0.0, 100.0)	(0.0, 100.0)	

[1]P-value from two-group t-test

c. Supplementary Analysis

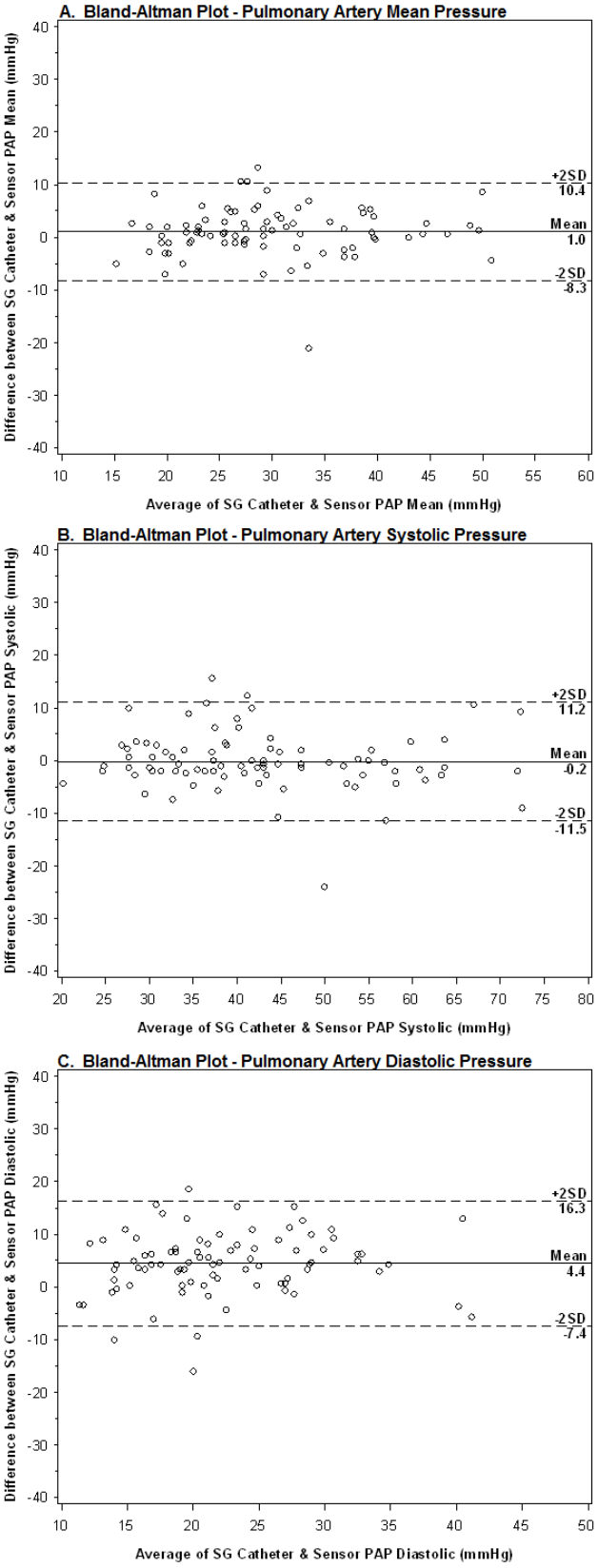
i. Randomized Access (Part 1) Additional Analyses

1. Sensor Performance Analysis

Comparative data of a subset of 43 patients who underwent 85 physician-initiated right heart catheterization (RHC) procedures for clinical reasons during the study were provided in the following Bland-Altman plot. As shown in the plot below (Figure 8), there was good concordance between the sensor and Swan-Ganz PA mean measurements with a mean difference (sensor minus SG) of 1.0 mmHg with limits of agreement from 10.4 mmHg to -8.3 mmHg. In these analyses, the limits of agreement refer to ±2STD (standard deviations) with respect to the difference in measurements between the two (2) techniques.

The following data excludes the data for eight (8) RHC procedures for which CardioMEMS identified a problem with sensor calibration or sensor implantation position. Consequently, these data may overestimate the correlation between sensor readings and Swan-Ganz PA mean pressure measurements.

Figure 8. Bland-Altman Plot – Pulmonary Artery Pressure Compared to RHC



2. DSRCs and Sensor Failures After 6 Month Follow-Up Visit

After the 6 month visit all 498 (100%) patients remaining in the study were free of DSRCs, as shown in Table 23. All DSRCs occurred in the immediate peri-implant time period indicating that there is minimal risk of a DSRC after 6 months.

Table 23. Device/System Related Complications after 6 Month Follow-Up Visit

	Consented Not Randomized	Treatment	Control	All Patients
After 6 Month Follow-up Visit				
Patients	0	244	254	498
Device/System Related Complication[1]				
Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
No		244 (100%)	254 (100%)	498 (100%)

[1]A device/system-related complication is an adverse event that is, or is possibly, related to the system (wireless pressure sensor or external electronics) and at least one the following: is treated with invasive means (other than intramuscular medication or a right heart catheterization with a Swan-Ganz measurement which is used for diagnostic purposes), results in the death of the patient, results in the explant of the device.

Of the total 498 patients still in the study at 6 months, all (100%) had operational sensors after 6 months as shown in Table 24.

Table 24. Pressure Sensor Failures After 6 Months Follow-Up Visit

	Treatment	Control	All Patients
After 6 Month Follow-up Visit			
Patients	244	254	498
Pressure Sensor Failure[1]			
Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)
No	244 (100%)	254 (100%)	498 (100%)

[1]A pressure sensor failure occurs when the sensor malfunctions to the point that no readings can be obtained from it after all attempts are exhausted including troubleshooting the system to rule out any problems with the electronic components.

3. All Cause Hospitalizations

This pre-specified analysis was intended to determine whether the reduction in HFR hospitalizations was offset by an increase in non-HFR hospitalizations.

During the 6 month primary effectiveness period, the Treatment group had 84 HFR hospitalizations compared to 120 HFR hospitalizations in the Control group. During this same period the Treatment group had a total of 232 hospitalizations and the Control group had a total of 263 hospitalizations. There were 148 non-HFR hospitalizations in the Treatment group vs. the 143 non-HFR hospitalizations in the Control group indicating a lack of increase in non-HFR hospitalizations in the Treatment group. See Table 25 below.

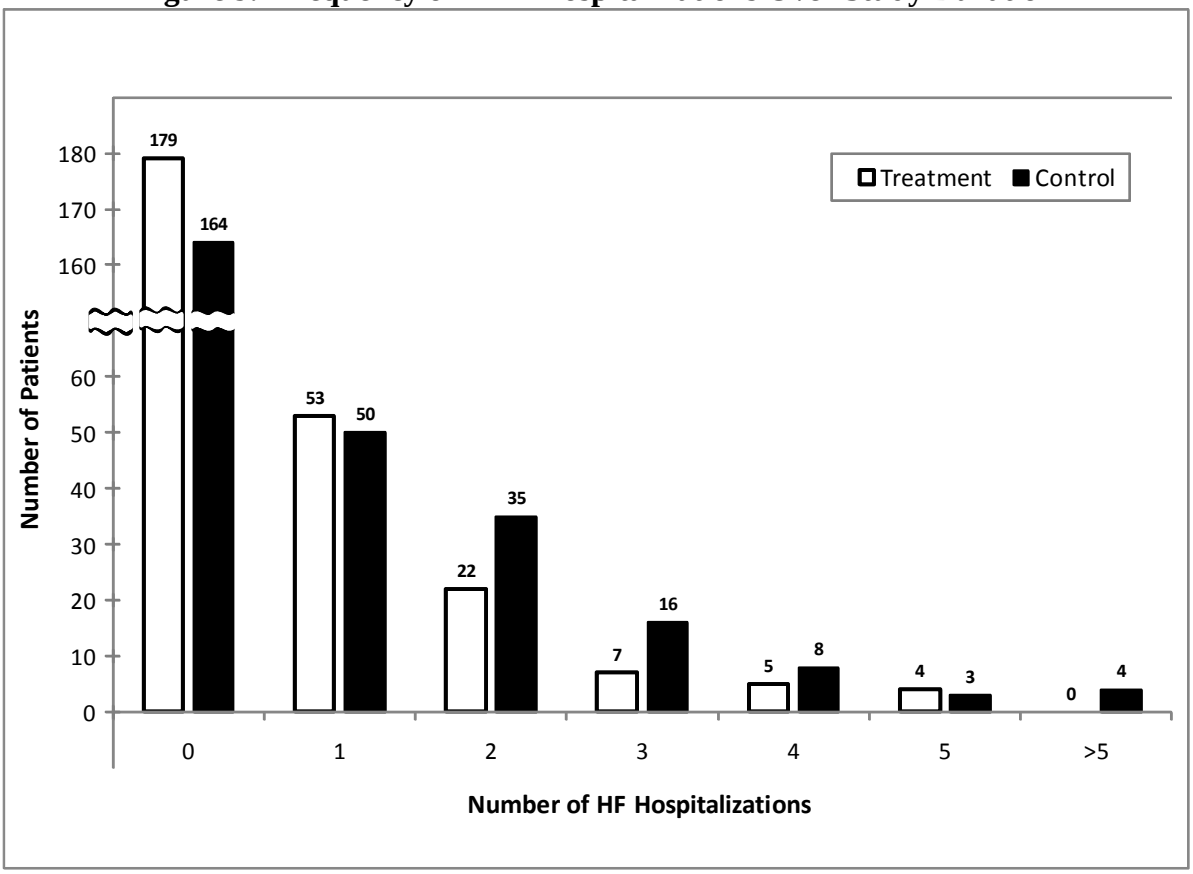
Table 25. Summary of CEC Hospitalization Adjudications

	Treatment hospitalizations (6-month rate)	Control hospitalizations (6-month rate)
6 Months		
All Cause Hospitalizations	232 (0.86)	263 (0.96)
HFR Hospitalizations	84 (0.32)	120 (0.44)
Non-HFR Hospitalizations	148 (0.55)	143 (0.52)

4. Frequency of HFR Hospitalizations

Figure 9 shows the number of patients who had 0, 1, 2, 3, 4, 5 or >5 hospitalizations over the entire follow-up period. As expected, increasing length of follow-up increases the risk that a patient would have at least one (1) hospitalization. Compared to the Control group, the Treatment group had more patients without HFR hospitalizations and fewer patients with multiple hospitalizations. Over the full duration of the Randomized Access (Part 1), the distribution of HFR hospitalizations generally favors the Treatment arm and the treatment effect does not appear to be driven by a single patient category.

Figure 9. Frequency of HFR Hospitalizations Over Study Duration



5. HF Medication Results Over the Randomized Access (Part 1) Duration

   Tables 26, 27, and 28 repeat the same medication analyses from baseline to the study duration (mean time = 15 months; max follow-up time = 31.5 months) and shows very similar patterns as the baseline to 6 month analyses. In addition to the results at 6 months, there were also more Treatment patients on nitrates compared to Control patients (38.1% vs. 23.6%) for full study duration. This was also true for hydralazine (24.1% vs. 14.6%). This medication data suggests that the changes in medication titration that occur by 6 months are maintained during long term follow-up.

Table 26. Proportion of Patients on HF Drug Therapy for Study Duration

HF Medication	Treatment (270)	Control (280)	All Patients (550)
ACE/ARB	190 (70.4%)	191 (68.2%)	381 (69.3%)
Beta Blocker	223 (82.6%)	233 (83.2%)	456 (82.9%)
Aldosterone Antagonist	118 (43.7%)	113 (40.4%)	231 (42.0%)
Nitrate	103 (38.1%)	66 (23.6%)	169 (30.7%)
Hydralazine	65 (24.1%)	41 (14.6%)	106 (19.3%)
Diuretic-Loop	248 (91.9%)	246 (87.9%)	494 (89.8%)
Diuretic-Thiazide-Standing	52 (19.3%)	44 (15.7%)	96 (17.5%)
Diuretic-Thiazide-PRN	41 (15.2%)	34 (12.1%)	75 (13.6%)

Table 27. Fraction of Maximal Dose: Change from Baseline to the Study Duration

	Baseline Mean±SD		Entire Blinded Randomized Follow-up Mean±SD		Change from Baseline Mean	
Medication	Treatment	Control	Treatment	Control	Treatment	Control
ACE/ARB	0.51±0.45 (n=174)	0.55±0.50 (n=181)	0.57±0.59 (n=174)	0.55±0.51 (n=181)	0.06	0.00
Beta Blocker	0.60±0.45 (n=214)	0.63±0.58 (n=226)	0.67±0.54 (n=214)	0.65±0.56 (n=226)	0.07	0.02

Table 28. Total Daily Dose: Change from Baseline to the Study Duration

	Baseline Mean±SD		Entire Blinded Randomized Follow-up Mean±SD		Change from Baseline Mean	
Medication	Treatment	Control	Treatment	Control	Treatment	Control
Aldosterone Antagonist	27.29±11.18 (n=90)	32.88±22.51 (n=96)	32.64±20.48 (n=90)	35.55±29.14 (n=96)	5.35	2.67
Nitrate	64.72±37.52 (n=54)	55.54±36.37 (n=46)	77.04±52.54 (n=54)	59.89±39.95 (n=46)	12.31	4.35
Hydralazine	148.0±115.4 (n=31)	112.1±67.30 (n=24)	158.1±108.3 (n=31)	156.9±111.4 (n=24)	10.08	44.79
Diuretic-Loop	98.82±76.34 (n=228)	100.1±75.19 (n=235)	123.8±105.7 (n=228)	111.4±90.38 (n=235)	24.94	11.33
Diuretic-Thiazide	3.40±1.88 (n=16)	3.24±2.17 (n=21)	4.54±3.61 (n=16)	2.85±2.26 (n=21)	1.14	-0.39
Diuretic-Thiazide PRN	3.13±1.23 (n=18)	3.47±1.74 (n=17)	3.06±1.30 (n=18)	4.00±2.93 (n=17)	-0.07	0.52

6. Survival Analysis

This was a pre-specified analysis that identified 15 deaths among 270 Treatment patients and 20 deaths among 280 Control patients up to the 6 month follow-up visit. Figure 10 depicts the Kaplan-Meier Patient Survival Plot up to 6 months. Table 29 lists how the CEC adjudicated the Randomized Access (Part 1) deaths.

Figure 10. Kaplan-Meier Patient Survival Plot up to 6 months

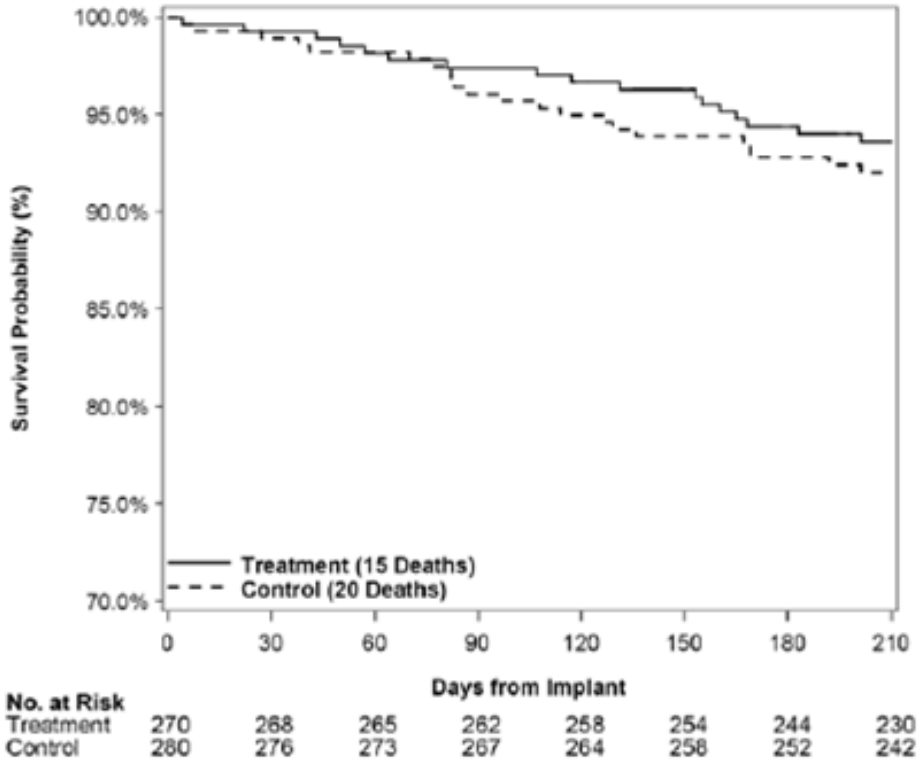


Table 29. CEC Adjudication of Mortality at 6 Months

	Treatment (270)	Control (280)	All Patients (550)
Total Subjects with Mortality	15 (5.6%)	20 (7.1%)	35 (6.4%)
Cause of Death			
Heart Failure	9 (3.3%)	6 (2.1%)	15 (2.7%)
Sudden Cardiac Death	3 (1.1%)	6 (2.1%)	9 (1.6%)
Cardiac Procedure[1]	0 (0.0%)	1 (0.4%)	1 (0.2%)
Cardiac-Other[2]	0 (0.0%)	1 (0.4%)	1 (0.2%)
Non-cardiac/non-vascular	3 (1.1%)	6 (2.1%)	9 (1.6%)

[1]Heart transplant
[2]Non-ischemic ventricular dysrhythmia

The death rates were similar between the Treatment and Control groups and the overall proportion of deaths was 6.4% through 6 months. The overall mortality rate in the current study compares reasonably well to published reports [1-17] of similar patient populations with advanced heart failure, prior heart failure hospitalization, and severe LV systolic dysfunction.

ii. Randomized Access (Part 1) Subgroup Analyses

1. Pre-Specified Analysis by Baseline Ejection Fraction

The only pre-specified subgroup analysis was with respect to baseline ejection fraction. Reduced ejection fraction was defined as EF < 40% and preserved ejection fraction was defined as EF ≥ 40%. The following tables summarize the baseline demographics in the Treatment and Control groups with respect to EF (reduced and preserved). Overall, there were no significant differences in baseline characteristics between the Treatment and Control patients in either reduced ejection fraction or preserved ejection fraction.

Table 30. Screening Demographics and Assessments – Reduced Ejection Fraction (EF<40%)

	Treatment (208)	Control (222)	All Patients (430)
Age (years)			
Mean±StdDev (N)	59.7±13.0 (208)	61.0±12.7 (222)	60.4±12.8 (430)
Median	61.0	62.0	61.0
(Min, Max)	(22.0, 88.0)	(24.0, 90.0)	(22.0, 90.0)
Gender			
Male	157 (75.5%)	170 (76.6%)	327 (76.0%)
Female	51 (24.5%)	52 (23.4%)	103 (24.0%)
Race			
White	142 (68.3%)	161 (72.5%)	303 (70.5%)
Black (of African Descent)	61 (29.3%)	53 (23.9%)	114 (26.5%)
Asian	0 (0.0%)	3 (1.4%)	3 (0.7%)
American Indian or Alaskan Native	2 (1.0%)	1 (0.5%)	3 (0.7%)
Other	3 (1.4%)	4 (1.8%)	7 (1.6%)
Ethnicity			
Hispanic	11 (5.3%)	11 (5.0%)	22 (5.1%)
Non-Hispanic	197 (94.7%)	211 (95.0%)	408 (94.9%)

	Treatment (208)	Control (222)	All Patients (430)
BMI			
Mean±StdDev (N)	30.2±6.0 (208)	30.1±6.4 (222)	30.1±6.2 (430)
Median	29.4	29.8	29.5
(Min, Max)	(17.9, 48.7)	(17.2, 55.1)	(17.2, 55.1)
BMI > 35			
Yes	44 (21.2%)	45 (20.3%)	89 (20.7%)
No	164 (78.8%)	177 (79.7%)	341 (79.3%)
Chest Circumference			
< 52	25 (12.0%)	34 (15.3%)	59 (13.7%)
≥52 & ≤65	19 (9.1%)	11 (5.0%)	30 (7.0%)
> 65	0 (0.0%)	0 (0.0%)	0 (0.0%)
NYHA Class			
Class I	0 (0.0%)	0 (0.0%)	0 (0.0%)
Class II	0 (0.0%)	0 (0.0%)	0 (0.0%)
Class III	208 (100%)	222 (100%)	430 (100%)
Class IV	0 (0.0%)	0 (0.0%)	0 (0.0%)
CRT or CRT-D			
Yes	82 (39.4%)	89 (40.1%)	171 (39.8%)
No	126 (60.6%)	133 (59.9%)	259 (60.2%)
ICD			
Yes	79 (38.0%)	87 (39.2%)	166 (38.6%)
No	129 (62.0%)	135 (60.8%)	264 (61.4%)
Ejection Fraction			
Mean±StdDev (N)	24.4±7.4 (208)	22.3±7.0 (222)	23.3±7.3 (430)
Median	25.0	20.0	25.0
(Min, Max)	(5.0, 37.0)	(5.0, 38.0)	(5.0, 38.0)
Heart Failure Type			
Ischemic Cardiomyopathy	127 (61.1%)	143 (64.4%)	270 (62.8%)
Non-Ischemic Cardiomyopathy	81 (38.9%)	79 (35.6%)	160 (37.2%)
Creatinine (mg/dl)			
Mean±StdDev (N)	1.43±0.50 (208)	1.36±0.42 (222)	1.39±0.46 (430)
Median	1.3	1.3	1.3
(Min, Max)	(0.7, 2.9)	(0.6, 2.8)	(0.6, 2.9)

	Treatment (208)	Control (222)	All Patients (430)
GFR (mL/min/1.73m²)			
Mean±StdDev (N)	61.1±23.4 (208)	62.6±23.6 (222)	61.9±23.5 (430)
Median	55.5	59.0	58.0
(Min, Max)	(25.0, 131.0)	(24.0, 152.0)	(24.0, 152.0)

Table 31. Screening Demographics and Assessments – Preserved Ejection Fraction (EF≥40)

	Treatment (62)	Control (57)	All Patients (119)
Age (years)			
Mean±StdDev (N)	66.8±11.4 (62)	65.4±12.1 (57)	66.1±11.7 (119)
Median	69.0	67.0	68.0
(Min, Max)	(37.0, 87.0)	(29.0, 89.0)	(29.0, 89.0)
Gender			
Male	37 (59.7%)	34 (59.6%)	71 (59.7%)
Female	25 (40.3%)	23 (40.4%)	48 (40.3%)
Race			
White	54 (87.1%)	43 (75.4%)	97 (81.5%)
Black (of African Descent)	7 (11.3%)	5 (8.8%)	12 (10.1%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)
American Indian or Alaskan Native	1 (1.6%)	2 (3.5%)	3 (2.5%)
Other	0 (0.0%)	7 (12.3%)	7 (5.9%)
Ethnicity			
Hispanic	3 (4.8%)	8 (14.0%)	11 (9.2%)
Non-Hispanic	59 (95.2%)	49 (86.0%)	108 (90.8%)
BMI			
Mean±StdDev (N)	32.9±7.7 (62)	34.5±9.4 (57)	33.6±8.6 (119)
Median	32.1	32.6	32.5
(Min, Max)	(20.4, 53.7)	(16.1, 73.8)	(16.1, 73.8)
BMI > 35			
Yes	20 (32.3%)	20 (35.1%)	40 (33.6%)
No	42 (67.7%)	37 (64.9%)	79 (66.4%)
Chest Circumference			

	Treatment (62)	Control (57)	All Patients (119)
< 52	17 (27.4%)	14 (24.6%)	31 (26.1%)
≥52 & ≤65	3 (4.8%)	6 (10.5%)	9 (7.6%)
> 65	0 (0.0%)	0 (0.0%)	0 (0.0%)
NYHA Class			
Class I	0 (0.0%)	0 (0.0%)	0 (0.0%)
Class II	0 (0.0%)	0 (0.0%)	0 (0.0%)
Class III	62 (100%)	57 (100%)	119 (100%)
Class IV	0 (0.0%)	0 (0.0%)	0 (0.0%)
CRT or CRT-D			
Yes	9 (14.5%)	9 (15.8%)	18 (15.1%)
No	53 (85.5%)	48 (84.2%)	101 (84.9%)
ICD			
Yes	9 (14.5%)	11 (19.3%)	20 (16.8%)
No	53 (85.5%)	46 (80.7%)	99 (83.2%)
Ejection Fraction			
Mean±StdDev (N)	50.5±9.2 (61)	50.8±9.2 (57)	50.6±9.1 (118)
Median	50.0	50.0	50.0
(Min, Max)	(40.0, 78.0)	(40.0, 70.0)	(40.0, 78.0)
Heart Failure Type			
Ischemic Cardiomyopathy	31 (50.0%)	31 (54.4%)	62 (52.1%)
Non-Ischemic Cardiomyopathy	31 (50.0%)	26 (45.6%)	57 (47.9%)
Creatinine (mg/dl)			
Mean±StdDev (N)	1.30±0.33 (62)	1.34±0.38 (57)	1.32±0.35 (119)
Median	1.3	1.3	1.3
(Min, Max)	(0.7, 2.1)	(0.7, 2.1)	(0.7, 2.1)
GFR (mL/min/1.73m^2)			
Mean±StdDev (N)	57.9±19.3 (62)	57.7±21.1 (57)	57.8±20.1 (119)
Median	53.5	49.0	53.0
(Min, Max)	(28.0, 123.0)	(29.0, 101.0)	(28.0, 123.0)

Patients with preserved ejection fraction had a mean EF of 51% and patients with reduced ejection fraction had a mean EF of 23%. Optimal medical treatment as recommended by ACC/ AHA HF guidelines for HF patients with preserved ejection fraction include

blood pressure and volume control, but is not as well defined as for patients with reduced ejection fraction. Nevertheless, this group had high rates of treatment with ACE/ARB and beta blockers.

Table 32. Baseline Neurohormonal Medications by Baseline Ejection Fraction

	Treatment	Control	All Patients
OPT at Baseline in Full Subject Population	(270)	(280)	(550)
ACE/ARB	205 (75.9%)	222 (79.3%)	427 (77.6%)
Beta Blocker	243 (90.0%)	256 (91.4%)	499 (90.5%)
OPT at Baseline in Reduced Ejection Fraction Population (EF<40%)	(208)	(222)	(430)
ACE/ARB	163 (78.4%)	176 (79.3%)	339 (78.8%)
Beta Blocker	193 (92.8%)	208 (93.7%)	401 (93.3%)
OPT at Baseline in Preserved Ejection Fraction Population (EF ≥ 40%)	(62)	(57)	(119)
ACE/ARB	42 (67.7%)	45 (78.9%)	87 (73.1%
Beta Blocker	50 (80.6%)	47 (82.5%)	97 (81.5%)

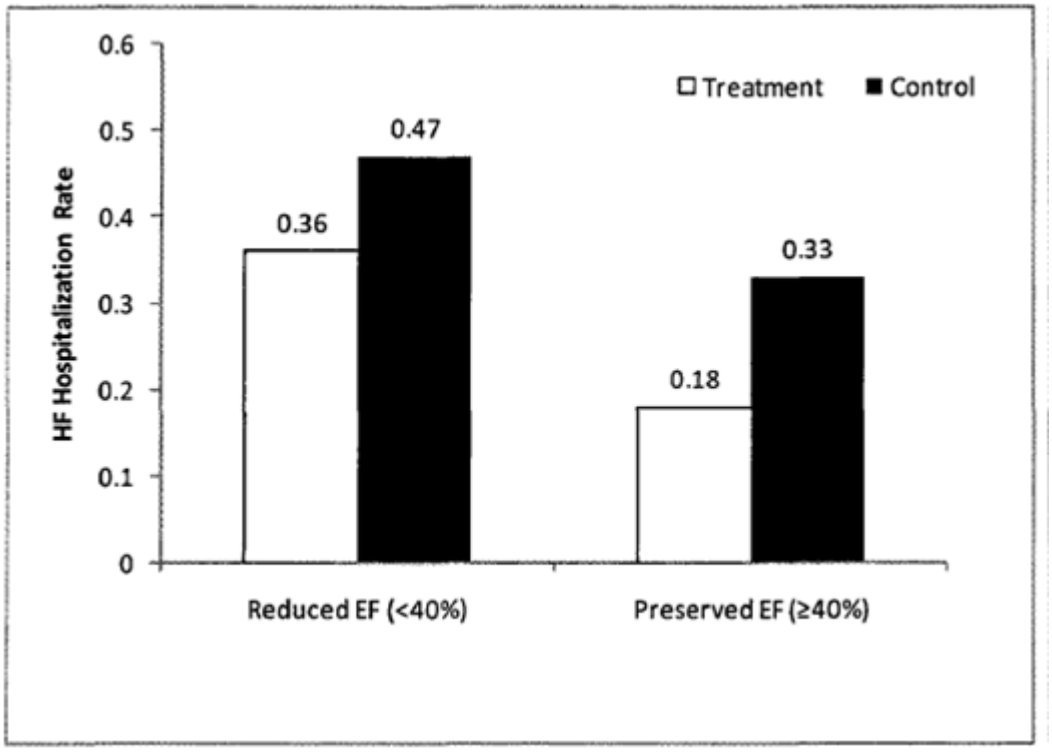
In patients with reduced ejection fraction, the Treatment group had 73 HF hospitalizations among 208 patients yielding a rate of 0.36 hospitalization/patient-6 months. In contrast, the Control group had 101 hospitalizations among 223 patients, yielding a rate of 0.47, hospitalization/patient-6 months, which was higher than the Treatment group.

In the patients with preserved ejection fraction, the overall rate of hospitalization tended to be lower than that observed with patients with reduced ejection fraction. Nonetheless, the treatment benefit was still significant. The Treatment group had 11 hospitalizations among 62 patients, yielding a rate of 0.18 hospitalizations/patient-6 months. In the Control group, there were 19 hospitalizations among 57 patients, yielding a rate of 0.33, which was higher than the Treatment group . These results suggest that HF management based on PAP is effective in reducing HF hospitalizations in patients with either reduced or preserved LV function.

Table 33. Analysis of Rate of HF Hospitalizations at 6 months by Baseline Ejection Fraction

	Treatment (270)			Control (280)		
	# Pts. (n)	# Hosp. (n)	Hosp. Rate (events/ patient-year)	# Pts. (n)	# Hosp. (n)	Hosp. Rate (events/ patient-year)
EF < 40%	208	73	0.36	222	101	0.47
EF ≥ 40%	62	11	0.18	57	19	0.33

Figure 11. Hospitalizations by Baseline Preserved and Reduced Ejection Fraction



2. Gender Analysis

A *post-hoc* analysis on HFR hospitalization rate was conducted and assessed according to gender.

Of the 550 implanted and randomized patients, 73% were male. In the Treatment group, the 6 month HFR hospitalization rate was 0.32 events/patient for both males and females. In the Control group, the 6 month HFR hospitalization rate was 0.52 events/patient for males and 0.17 events/patient for females. Significant interaction between

gender and treatment was detected for this data set, raising the possibility that the device has a differential effect on HFR hospitalizations for men and women.

Table 34. HFR Hospitalizations at 6 Months Stratified on Gender

	Treatment			Control		
	Patients	# Hosp.	Hosp. Rate (events/ patient-6 mo.)	Subjects	# Hosp.	Hosp. Rate (events/ patient-6 mo.)
Male	194	60	0.32	205	106	0.53
Female	76	24	0.32	75	14	0.19

However, compared to the Treatment group, more than twice as many women in the Control group died within 6 months (7 Control female deaths vs. 3 Treatment female deaths). This raises the possibility of the competing risk of death contributing to the reported difference in HFR hospitalization outcomes with respect to gender.

Table 35. HFR Hospitalizations over Original Study Duration Stratified on Gender

	Treatment			**Control**		
	Subjects	**# Hosp.**	**Hosp. Rate (Annualized)**	**Subjects**	**# Hosp.**	**Hosp. Rate (Annualized)**
Male	194	114	0.45	205	214	0.83
Female	76	44	0.47	75	40	0.43

iii. Results from the Entire Randomized Access Period

1. HF Hospitalizations

During the entire Randomized Access period (Part 1), the rate of HF hospitalizations was 33% lower in the Treatment group than in the Control group (0.46 vs. 0.68 annualized HF hospitalization rates, HR 0.67, 95%CI 0.55-0.80) (Table 36). The magnitude of the effect during the entire Randomized Access period was slightly larger than that seen during the 6-month primary endpoint period (33% vs. 28%), indicating durability of the treatment effect. The number needed to treat (NNT) per year to prevent one (1) HF hospitalization was four (4). For every 100 patients treated, 23 HF hospitalizations would be prevented per year.

Table 36. HF Hospitalization Rates During Randomized Access

	Number of HF Hospitalizations	Annualized HF Hospitalization Rate	Hazard Ratio (95% CI)	NNT Per Year to Prevent One HF Hospitalization
Treatment Group (n=270)	182	0.46	0.67 (0.55-0.80)	4
Control Group (n=280)	279	0.68		

2. Mortality

   The proportion of patients who died in the Treatment group (18.5%) was smaller than in the Control Group (22.9%) with a relative risk reduction of 20% (HR 0.80, 95% CI 0.55 – 1.15).

3. Freedom from Death or First HF Hospitalization

   The proportion of patients who died or had at least one (1) HF hospitalization in the Treatment group (44.8%) was smaller than in the Control Group (51.8%) with a relative risk reduction of 23% (HR 0.77, 95% CI 0.60 – 0.98).

4. All Cause Hospitalizations

   All cause hospitalizations were reduced in the Treatment group (554 in the Treatment group vs. 672 in the Control group, HR 0.84, 95% CI 0.75 – 0.95). The NNT per year to prevent one all cause hospitalization was four (4). For every 100 patients treated, 26 all cause hospitalizations would be prevented per year.

5. Death or All Cause Hospitalizations

   Death or all cause hospitalizations were reduced in the Treatment group (604 in the Treatment group vs. 736 in the Control group, HR 0.84, 95% CI 0.76 – 0.94). The NNT per year to prevent one death or all cause hospitalization was four (4). For every 100 patients treated, 29 deaths or all cause hospitalizations would be prevented per year.

3. <u>Open Access (Part 2) Longitudinal and Supplemental Ancillary Analyses</u>

The Open Access (Part 2) analyses are ancillary analyses conducted on follow-up data obtained during Part 2 of the study. At this time, nurse communications had ceased and patients randomized to the Control group in the Randomized Access (Part 1) were managed with knowledge of PA pressures. The analyses were specified prior to unblinding the additional follow-up data, but were not specified prior to initiation of the study or to collection of the data. Furthermore, because

they were not planned analyses, there exists a potential inequality of baseline covariates and demographics between the Former Control and Former Treatment groups in Part 2 of the study. Finally, there was likely a non-random patient drop-out rate during part 1 of the study.

a. Longitudinal Analyses

Comparison of the HFR hospitalization rates between Former Control (Part 2) and Control (Part 1) assessed whether providing PA pressure information, in the absence of nurse communications, led to a lowering of HFR hospitalization rates. If the effect of HFR hospitalization rate observed in Part 1 was primarily due to use of the PA pressures, one would expect the HFR hospitalization rate in Control group patients to decrease after the transition from Part 1 to Part 2. Shown in Tables 37 and 38 below, the rate of HFR hospitalization decreased from 0.68 HFR hospitalizations per patient year for Control patients in Part 1 to 0.36 HFR hospitalization per patient year for Former Control patients in Part 2 (HR 0.52, $p < 0.0001$).

Table 37. Comparisons of HF Hospitalization Rates using Andersen-Gill Model with Frailty

Comparison	Hazard Ratio (95%) Confidence Interval)	p-values
1. Former Control to Control	0.52 (0.40 – 0.69)	<0.0001
2. Former Treatment to Treatment	0.93 (0.70 – 1.22)	0.5838
3a. Former Control to Former Treatment	0.80 (0.56 – 1.14)	0.2178
3b. Former Control to Former Treatment vs. Control to Treatment	0.56 (0.38 – 0.83)	0.0040
4. Former Control to Control vs. Former Treatment to Treatment	0.56 (0.38 – 0.83)	0.0040
Results from Andersen-Gill Model with Frality comparing HF hospitalization (HFH) rates.		

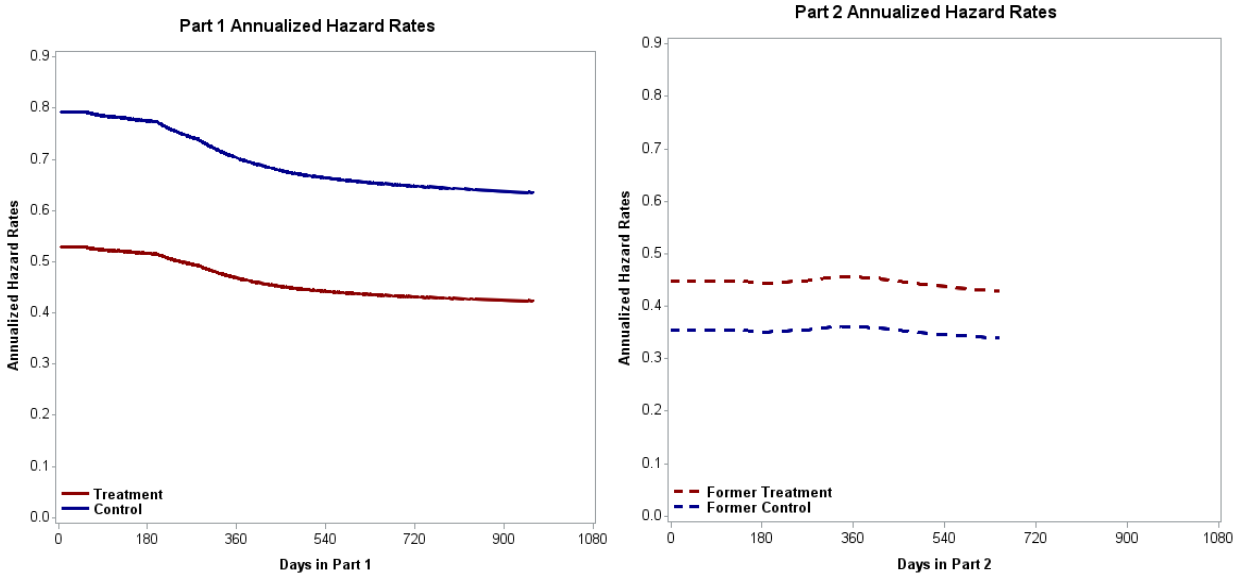
Table 38. Number of Patients, HFR Hospitalizations, and HFR Hospitalization Rates

	N	#HFH	HFH Rate (HFH/pt-yr)
Treatment	270	182	0.48
Former Treatment	177	78	0.45
Control	280	279	0.68
Former Control	170	64	0.36
Results from Andersen-Gill Model with Frailty comparing HFH rates.			

Note: The estimated HFR hospitalization per patient-year was calculated based on the regression parameters from the AG model and by setting the baseline hazard to the empirical Control HFR hospitalization rates in Part 1 (i.e., # HFR hospitalization / patient follow-up x 360 in Part 1).

The following plots (as shown in Figure 12) depict the Annualized Hazard Rates for the results from the four (4) longitudinal comparisons. The AHR difference between Former Control and Former Treatment becomes relatively small after all patients received investigator knowledge of PA pressure, but were no longer the subject of nurse communications. The AHR's of Treatment in Part 1 and Part 2 remain similar. Additionally, there was a large decrease in AHR for Controls after the transition from Part 1 to Part 2 when they began to receive PA pressure based treatments after the transition.

Figure 12. Annualized Hazard Rates



The results of all the longitudinal analyses were consistent with the primary endpoint analysis for Part 1 of the study. They suggest:

- a reduction in HFR hospitalization rates from Control to Former Control;
- no difference in HFR hospitalization rates between Treatment and Former Treatment
- no difference in HFR hospitalization rates between Former Control and Former Treatment; and
- a difference in the change in HFR hospitalization rates in Control group (Part 2 vs. Part 1) as compared to the change in HFR hospitalization rates in the Treatment (Part 2 vs. Part 1).

The impact of the treatment is a reduction of the HFR hospitalization rate by 0.20-0.32 per patient-year. This was calculated as the difference in HFR hospitalization rates between the Treatment (0.48) and Control (0.68) and the difference between the Former Control (0.36) and Control (0.68). However, these results should be interpreted with caution because the analyses are ancillary.

Despite the limitations of the longitudinal analyses, these data are compelling in terms of supporting the effectiveness of the device.

b. Supplementary Analysis

i. Survival

As seen in Figures 13 and 14 below, the mortality benefit was unaltered in the Open Access (Part 2) over Randomized Access (Part 1) (HR=0.80, p=0.23).

Figure 13. Patient Survival over Part 1

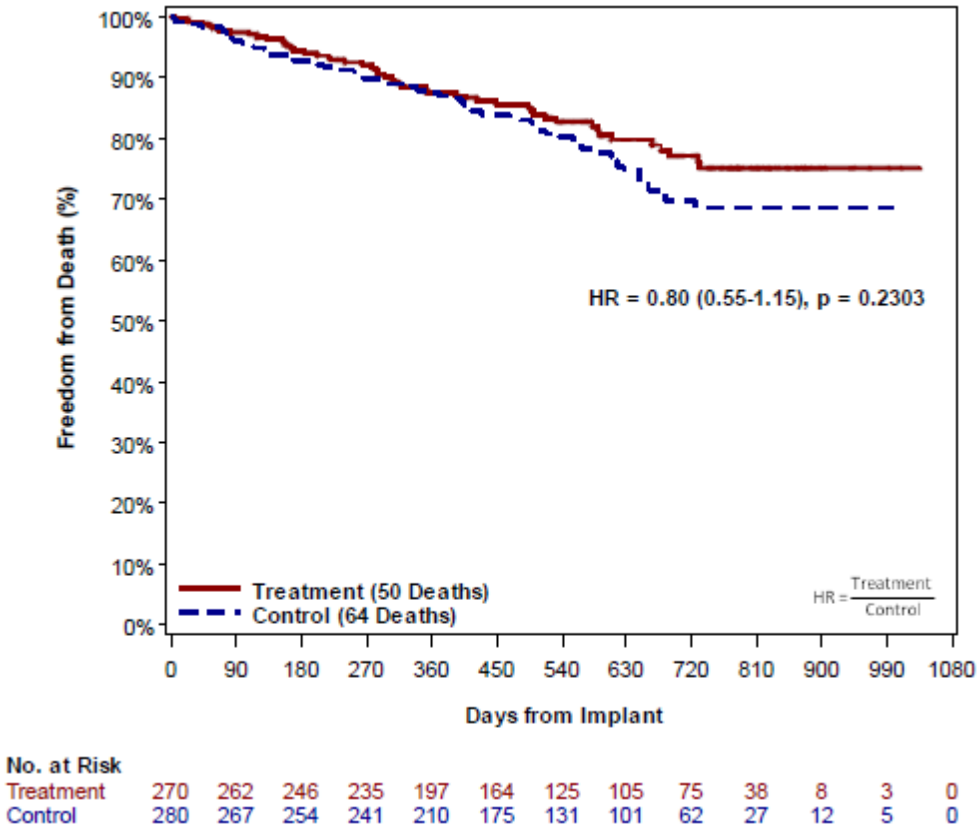
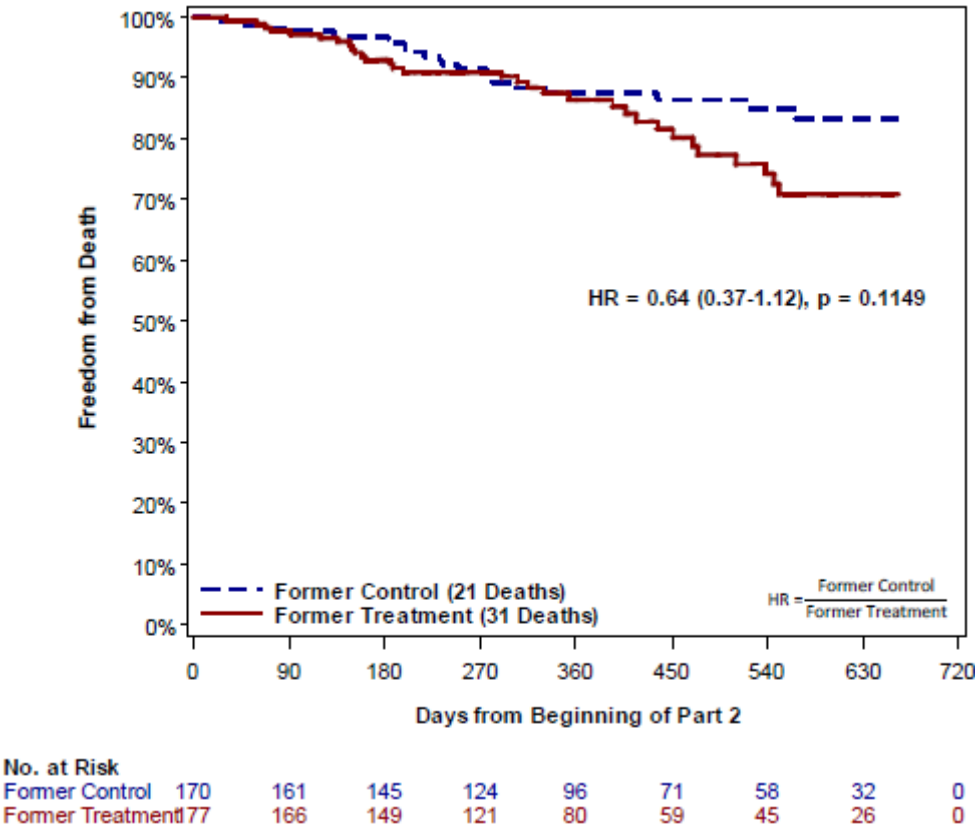


Figure 14. Patient Survival over Part 2



ii. Minnesota Living with Heart Failure Questionnaire (MLHFQ)

The effect of the device on Quality of Life (QoL) was analyzed using the Minnesota Living with Heart Failure Questionnaire (MLHFQ). A QoL benefit was noted at 6 months; however; it did not reach statistical significance at 12 months, which may have been due to the reduction in sample size.

Table 39. Quality of Life: MLHFQ at 6 Months

	Treatment (270)	Control (280)	All Patients (550)	p-value[1]
6 Month Follow-up – Total Score				
Mean±StdDev (N)	45.2±26.4 (229)	50.6±24.8 (236)	48.0±25.7 (465)	0.0236
Median	45.0	52.0	49.0	
(Min, Max)	(0.0, 100.0)	(0.0, 100.0)	(0.0, 100.0)	

[1]P-value from two-group t-test

Table 40. Quality of Life: MLHFQ at 12 Months

	Treatment (270)	Control (280)	All Patients (550)	p-value[1]
12 Month Follow-up – Total Score				
Mean±StdDev (N)	46.4±26.0 (155)	50.1±25.1 (169)	48.3±25.5 (324)	0.1992
Median	45.0	53.0	50.5	
(Min, Max)	(0.0, 100.0)	(0.0, 98.0)	(0.0, 100.0)	

[1]P-value from two-group t-test

c. Gender Analysis

A composite of time to death or first HFR hospitalization was performed using a Cox proportional hazard model in a competing risk analysis over Part 1 and the full duration of Part 1 plus Part 2. In addition, an Anderson-Gill Model with Frailty, Anderson Gill Model with Robust Sandwich Estimates (RSE), and Negative Binomial Regression using an endpoint of time to HFR hospitalization or death was performed on Part 1 and Part 1+Part2. As seen in the italicized rows in Table 41 below, all the competing risk analyses taking death into account as a competing risk show that there was no evidence of a treatment-by-gender interaction if a p-value of 0.05 is used. However, when analyses for interaction by gender are conducted, a p-value of 0.15 is typically used because the analysis is typically not powered appropriately. When considering a p-value of 0.15, there was some evidence of treatment-by-gender interaction in the competing risk analyses under the following models:

- AG Model with Frailty for Part 1
- NB Regression for Part 1
- AG Model with Robust Sandwich Estimate for Part 1 + Part 2
- GEE NG Regression for Part 1 + Part 2

Table 41. Results of treatment by gender interaction using different statistical models

Models	Estimate	SE	p-value
Part 1			
Cox Model: Endpoint of first HFR hospitalization or Death	*-0.113*	*0.289*	*0.6968*
Cox Model: Endpoint of first HFR hospitalization	-0.330	0.327	0.3131
AG Model with Frailty: Endpoint of HFR hospitalization or Death	*-0.373*	*0.239*	*0.1211*
AG Model with Frailty: Endpoint of HFR hospitalization	-0.531	0.262	0.0459
AG Model with RSE: Endpoint of HFR hospitalization or Death	*-0.433*	*0.316*	*0.1712*
AG Model with RSE: Endpoint of HFR hospitalization	-0.577	0.360	0.1094
NB Regression: Endpoint of HFR hospitalization or Death	*-0.412*	*0.242*	*0.0896*
NB Regression: Endpoint of HFR hospitalization	-0.573	0.191	0.0027
Part 1 + Part 2			
Cox Model: Endpoint of first HFR hospitalization or Death	*-0.204*	*0.249*	*0.4121*

Models	Estimate	SE	p-value
Cox Model: Endpoint of first HFR hospitalization	-0.427	0.284	0.1331
AG Model with Frailty: Endpoint of HFR hospitalization or Death	*-0.376*	*0.274*	*0.1697*
AG Model with Frailty: Endpoint of HFR hospitalization	-0.588	0.271	0.0301
AG Model with RSE: Endpoint of HFR hospitalization or Death	*-0.477*	*0.274*	*0.0816*
AG Model with RSE: Endpoint of HFR hospitalization	-0.642	0.313	0.0399
GEE NB Regression: Endpoint of HFR hospitalization or Death	*-0.488*	*0.283*	*0.0841*
GEE NB Regression: Endpoint of HFR hospitalization	-0.761	0.319	0.0172

However, these analyses also indicate an HFR Hospitalization benefit in men but no such benefit in women. The results of AG Model with Frailty are shown below in Table 42.

Table 42. The Treatment vs. Control effects by Gender over Part 1 and over Part 1+ Part 2 under different models

Males	Hazard Ratio	p-value
Part 1 (Treatment vs. Control)		
AG Model with Frailty: Endpoint of HFR hospitalization or Death	*0.67*	*0.0007*
AG Model with Frailty: Endpoint of HFR hospitalization	0.64	0.0004
Part 1 + Part 2 (Former Control vs. Control)		
AG Model with Frailty: Endpoint of HFR hospitalization or Death	*0.70*	*0.0176*
AG Model with Frailty: Endpoint of HFR hospitalization	0.53	<0.0001
Females	Hazard Ratio	p-value
Part 1 (Treatment vs. Control)		
AG Model with Frailty: Endpoint of HFR hospitalization or Death	*0.99*	*0.9440*
AG Model with Frailty: Endpoint of HFR hospitalization	1.07	0.7584
Part 1 + Part 2 (Former Control vs. Control)		
AG Model with Frailty: Endpoint of HFR hospitalization or Death	*0.80*	*0.4512*
AG Model with Frailty: Endpoint of HFR hospitalization	0.61	0.1482

Figures 15 and 16 depict the Freedom from HFR Hospitalization and Freedom from Death for Men and Women over the Full Randomized Period (Part 1). Figure 17 below depicts the composite endpoint of Freedom from HFR Hospitalization or Death for Men and Women over the Full Randomized Period (Part 1). They illustrate the apparent difference in treatment effect by gender. As seen in Figure 15, for HFR hospitalizations alone Treatment and Control women have similar outcomes. However as seen in Figure 16, Control women had an increased early mortality creating a competing risk for HFR hospitalizations (i.e., fewer Control women were alive to have HFR hospitalizations). Figure 17 examines Freedom from HFR Hospitalization or Death and indicates a non-significant trend favoring women in the Treatment group.

Figure 15. Freedom from HFR Hospitalization Over the Full Randomized Period (Part 1).

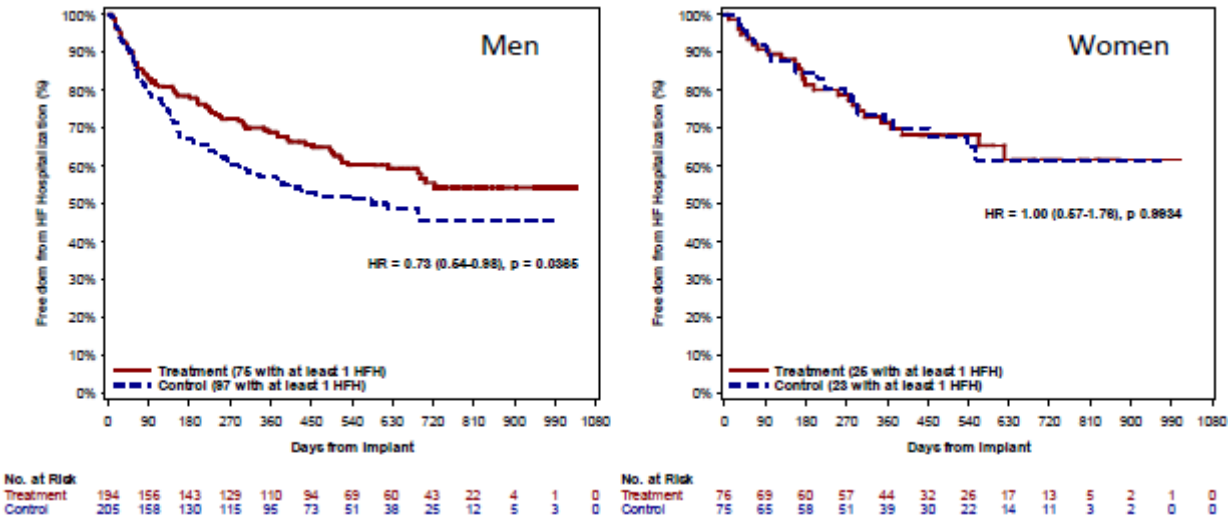


Figure 16. Freedom from Death Over the Full Randomized Period (Part 1).

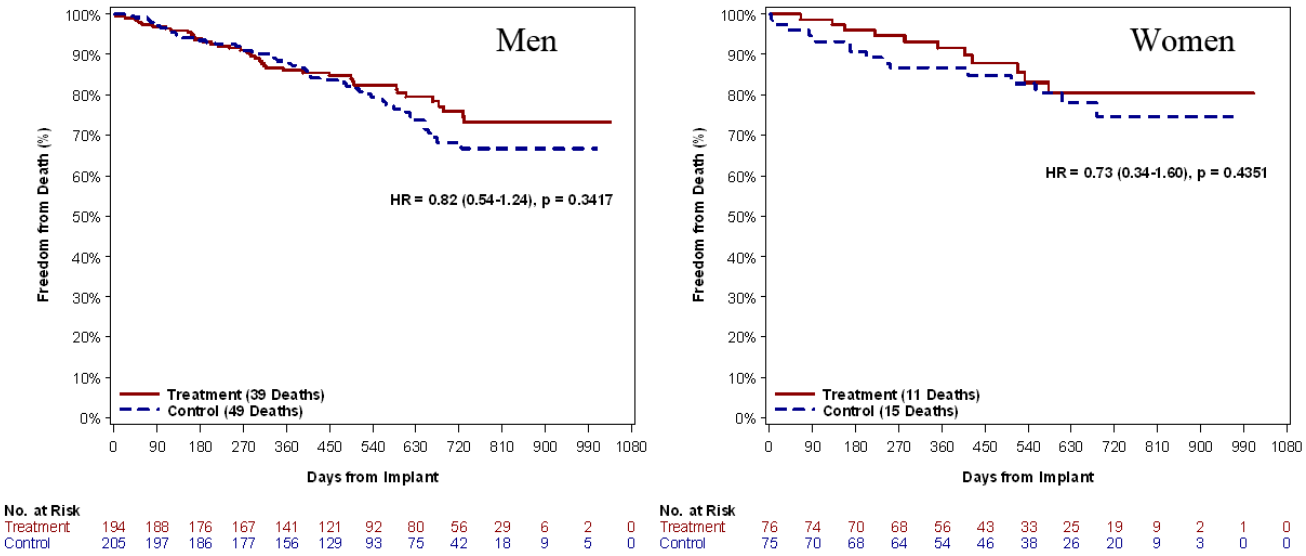
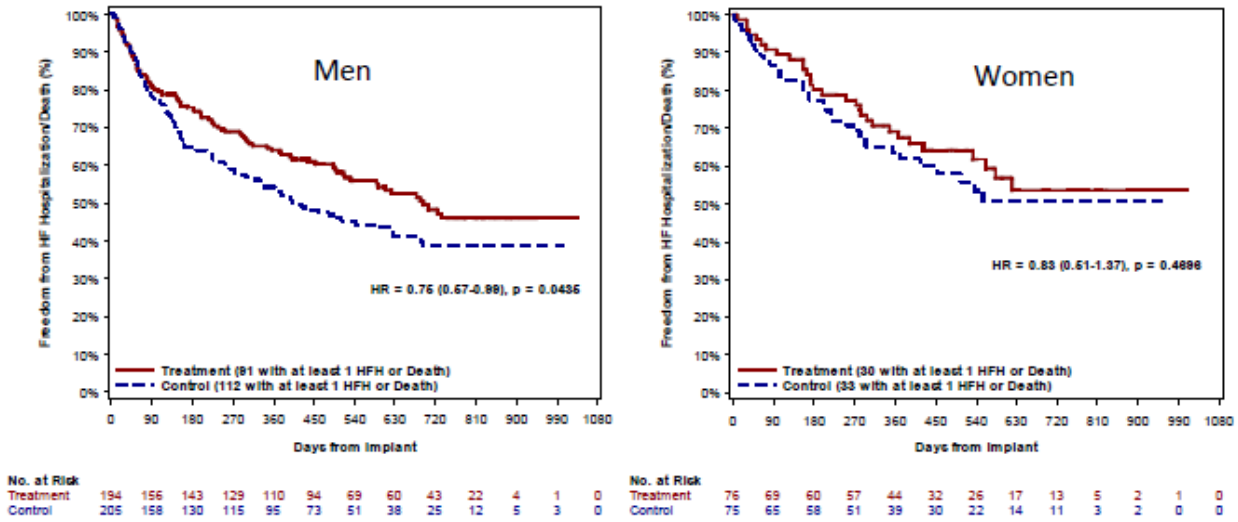


Figure 17. Freedom from HFR Hospitalization or Death Over the Full Randomized Period (Part 1).



HR, Confidence Intervals and p-value from Cox proportional hazards model

There appears to be a limited treatment effect (HFR hospitalization rate reduction) in females. It is unclear whether this was due to the number of women in the study (N = 151) and few events in the trial, the competing risk of death in Control group women, or if it was due to the poor device efficacy among women. However, there seems to be no plausible explanation for the difference other than the small number of women and events in the study. Clarity will be sought by continuing to evaluate the treatment effect (HFR hospitalization rate reduction) in females in a post-approval Study.

d. Clinical Analysis

The majority of Treatment group subjects (N=171) were, at some point, the target of nurse communications. Two (2) cardiologists, acting independently of each other, assessed the concordance of the recommendations included in nurse communications with changes in medications recorded in the case report forms and the cardiologists were in agreement in >99% of cases. The cardiologists determined that any change that followed a nurse communication, and was concordant with any recommendation contained in the nurse communication, potentially exerted some influence on the prescribing investigator. The analysis determined that there were 125 communications that included a recommendation that was followed within 7 days by a concordant change in medications. Three (3) communications were followed by two (2) concordant medication changes within the 7 day window for a total of 128 concordant medication changes.

Table 43. Concordant Medication Changes Within 1, 2, 3, or 7 Days of a Nurse Communication

		Concordant Use of Drugs Consistent with Study Protocol and Hypothesis		Concordant Use of Drugs Not Consistent with Study Protocol and Hypothesis		No Concordant Medication Change
		Diuretics	Nitrates	Neurohormonal Antagonists	Hydralazine	
1-Day Window	First 6 Months	35	4*	2*	2	218
	Full Randomized Access	60	4*	2*	3	357
2-Day Window	First 6 Months	42	4*	3*	2	210
	Full Randomized Access	70	4*	3*	3	346
3-Day Window	First 6 Months	44	4*	3*	2	208
	Full Randomized Access	78	4*	3*	4	337
7-Day Window	First 6 Months	64	11*#	7*^	3^#	178
	Full Randomized Access	104	11*#	7*^	6^#	300

* One email (06-023 on 7-29-08) led to 2 concordant changes (nitrate & ACE inhibitor) within 1-day window during 1st 6 months
^ One email (030-002 on 7-7-08) led to 2 concordant changes (hydralazine & ACE inhibitor) within 7-day window during 1st 6 months
# One email (48-001 on 6-12-08) led to 2 concordant changes (Nitrate & HDZ) within 7 day window during 1st 6 months

As seen in Table 43 above, there were 10 concordant changes not consistent with the study protocol and hypothesis. Four (4) of these changes were considered to be clinically trivial. Based on the results of large-scale clinical trials and using conservative assumptions, the total effect of the six (6) concordant changes not consistent with the study protocol and hypothesis would have been to prevent approximately 0.73 hospitalizations for heart failure during the first 6 months of randomized access in the patients randomized to the Treatment group. The observed difference in the number of HFR hospitalizations between the two (2) groups during the first 6 months of randomized access was 36. Therefore, during the first 6 months of randomized access, the cardiologists estimated that approximately 2.0% (0.73/36) of the treatment effect may have been related to nurse communications that recommended changes not consistent with the study protocol and hypothesis.

Additionally, if adjustments are made for the background rate of use, the cardiologists estimated that approximately 0.9% (0.33/36) of the treatment effect seen during the first 6 months of Randomized Access may have been related to nurse communications that recommend changes in diuretics and nitrates. If all concordant medication changes are considered together, the

cardiologists estimated 1.06 (0.73 + 0.33) hospitalizations for heart failure, or 2.9% (1.06/36) of the observed treatment difference seen during the first 6 months of Randomized Access may have been related to nurse communications.

Any intervention in the Treatment group involving correspondences that had the potential to alter therapy (regardless of whether the alteration is consistent with the protocol) has the potential to introduce bias. This analysis estimates the effect of nurse communications relative to the effect of the device in reducing HFR hospitalizations. It is difficult to ascertain the likelihood that these numbers are accurate representations of the relative contributions to the observed treatment effect in the Randomized Access Period of the Study (Part 1).

e. Part 2 Propensity Score Analysis

The matched datasets were provided to an independent 3rd party data analysis center for outcome analyses. The datasets demonstrated a consistent reduction in the rate of HFR hospitalization in the Treatment No Nurse Communication (TNNC) group as compared with the rate in the propensity-matched controls using negative binomial procedure over the 30 matched datasets.

Based on the 30 sets of matched data generated from the reduced propensity score (PS) model, the minimum reduction in the rate of HFR hospitalization observed from the 30 data sets is 47.8% (95% CI from 33.9% to 58.8%) and the maximum reduction in the rate of HFR hospitalization observed from the 30 data sets is 48.9% (95% CI from 35% to 59.8%) in the TNNC group as compared the rate in the Propensity-matched control group.

Based on the 30 sets of matched data generated from the PS model with all covariates, the minimum reduction in the rate of HFR hospitalization observed from the 30 data sets is 43.2% (95% CI from 29.8% to 54%) and the maximum reduction in the rate of HFR hospitalization observed from the 30 data sets is 50.8% (95% CI from 36.2% to 62.1%) in the TNNC group as compared the rate in the Propensity-matched control group.

The results demonstrated a consistent reduction in the rate of HFR hospitalizations in the TNNC as compared with the rate in the propensity-matched controls using Part 1 study data. The results are consistent with original study results and longitudinal analyses.

Even though PS matching can balance observed baseline covariates between two (2) groups, they cannot balance unmeasured characteristics and confounders. Furthermore, there may be selection bias when matching patients between the TNNC and Control Groups. Subjects placed in the

TNNC Group did not have a nurse communication, a possible indication that these patients were healthy enough to not warrant a nurse communication. This potential non-random selection bias limits the conclusions that can be drawn definitively from the propensity score analysis.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 64 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

The first advisory meeting of the Circulatory Systems Device Panel for the CardioMEMS HF Monitoring System was held on December 8, 2011. Based on this panel meeting and FDA's remaining concerns, additional information was requested to support safety and effectiveness. Information from this advisory meeting can be found on FDA's website at the following: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM283470.pdf. Upon response to these concerns a second advisory meeting was scheduled.

A second advisory meeting held on October 9, 2013, the Circulatory Systems Device Panel voted 11-0 that there is reasonable assurance the device is safe, 7-4 that there is not reasonable assurance that the device is effective, and 6-4 (1 abstain) that the benefits of the device do outweigh the risks in patients who meet the criteria specified in the proposed indication. Information from the advisory meeting can be found on FDA's website at the following: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM370995.pdf.

B. FDA's Post-Panel Action

Regarding the 2nd Panel Meeting, FDA disagrees with the Panel Vote that there is not reasonable assurance that the device is effective. FDA acknowledges that, when taken individually, each analysis has its limitations. However, when considering the totality of effectiveness data, the consistency of the results indicate a positive

treatment effect in reducing HFR hospitalizations. This positive treatment effect seen in the Open Access (Part 2) of the study also agrees with the positive treatment effect seen in the Randomized Access (Part 1). However, because of the confounding effect of the nurse communications from Part 1 and the limitations of the ancillary analyses from Part 2, there remains some uncertainty regarding the magnitude of that positive effect. A rigorous Post Approval Study will be conducted with the goal of adding certainty around the magnitude of the positive treatment effect.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary endpoint for the effectiveness analysis from Part 1 of the study was met. However, the primary effectiveness endpoint analysis was confounded by nurse communications that included patient-specific treatment recommendations to study investigators. A series of ancillary analysis using Part 2 study data was conducted to further support approval and included:

- Four longitudinal analyses which concluded that HFR hospitalization rates in Former Control patients in Part 2 of the study decreased to levels comparable to the HFR hospitalization rates in Treatment group patients whose PA pressures were available throughout the study.

- A propensity score analysis of the Part 1 data that excluded Treatment group patients who were the subject of a patient-specific treatment recommendation. The analysis concludes HFR hospitalizations in patients who had not been the target of nurse communications is lower than that of propensity score – matched Control group patients.

In addition to the ancillary effectiveness analyses, a gender analysis was conducted to address a concern regarding a statistically significant treatment-by-gender interaction. The gender analysis, which used a composite of time to death or first HFR hospitalization, determined that there was not a qualitative and quantitative treatment-by-gender interaction when using a p value cut-off of 0.05. However, if the more typically used p-value cut-off of 0.15 is used, the interaction remains. It seems that the effectiveness in women in reducing HFR hospitalization rates is limited. It is unclear whether this limited treatment effect in females is due to the small number of females enrolled in the study, or if it can be attributed to differences in device effectiveness among men and women.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in the clinical studies to support PMA approval as described above. At 6 months follow-up as well as for the full study duration, the absence of device or system related complications among the Treatment and Control groups was

significant ($p<0.0001$), indicating device usage during the study was very safe and continued after the primary endpoint time interval of 6 months.

At 6 months follow-up as well as for the full study duration, there were no sensor failures ($p<0.0001$). There were no device related pulmonary thromboembolisms or pulmonary infarcts over the study duration.

There were no new adverse events observed during Part 2 of the study and the safety profile of the device remains positive.

C. Benefit-Risk Conclusions

The probable benefits outweigh the probable risks because the device has been shown to be very safe, and the totality of the effectiveness data consistently points to a positive treatment effect. Even if there remains some uncertainty around the magnitude of the treatment effect, the device is safe enough that even a more modest treatment effect than that observed in the pre-market studies would result in a favourable benefit/risk profile.

The primary safety endpoint was easily met. The primary effectiveness endpoint suggests that the device markedly reduces the heart failure related hospitalization rate. However, the reliability of the primary effectiveness endpoint analysis is questionable because of the confounding effects of patient-specific treatment recommendations made by the nurses to the study investigators. The "Longitudinal Analyses of Heart Failure Hospitalizations over the Randomized and Open Access Periods (Part 1 and Part 2)" are compelling evidence that supports device effectiveness. The follow-up on the "non-biased" original Control group is similar to a "cross-over" trial (in which a device is implanted but not "turned-on" initially and at a later time is activated). After transition to Open Access (Part 2), physician knowledge of PA pressure to guide or alter therapeutic regimens had a dramatic effect on the former Control group. Hospitalization rates were reduced by 48%. Consistent with the effectiveness of the device was the finding that the former Control group with intervention had a hospitalization rate indistinguishable from the continuing Treatment group. In addition, the "Clinical" and "Propensity Score Analysis" confirmed the assessment that the CaridioMEMS device results in reduced HF related hospitalizations.

Based on a subgroup analysis, the benefit/risk profile for the device in women is not as favourable as that in men because of the apparently diminished effectiveness in women. However, because the lack of a physiological explanation for the apparent diminished effectiveness in women, the small number of women enrolled in the premarket study, and the device's favourable safety profile, it is reasonable for the device to be used in women while the results of a Post-Approval Study corroborate whether the observed diminished effectiveness is present in a larger cohort of women.

Based on available information and preponderance of data, this device is safe and appears effective in reducing hospitalizations in the target population. In light of the

demonstrated small risk, the benefit/risk evaluation is favourable. A Post-Approval Study is planned to ascertain the magnitude of the treatment effect with more precision and to assure that no contrary evidence arises with broad clinical use of the device. Further gender analysis is warranted, but there is no obvious clinical basis or indication from current literature that suggest therapy based on knowledge of PA pressures in a female HF population should prove less effective than in a male HF population.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. It is important to consider the totality of effectiveness data presented. Although each analysis on its own has its flaws and limitations, the consistency and concordance of the results indicate a positive treatment effect in reducing HFR hospitalizations. However, the magnitude of the positive treatment effect remains unclear.

It also remains unclear whether the limited treatment effect in females is due to the small number of females enrolled in the study or if it can be attributed to differences in device effectiveness among men and women.

FDA intends to pursue both of these issues in a Post Approval Study to further assess the magnitude of the treatment effect and the potential gender inequality in treatment effect.

XIII. CDRH DECISION

CDRH issued an approval order on May 28, 2014. The final conditions of approval cited in the approval order are described below.

1. *Newly Enrolled Champion:* This study will be conducted as per protocol dated March 21, 2014, Version 1.0. The study will be a prospective, multi-center, open-label trial conducted in the United States to examine the safety and effectiveness of CardioMEMS™ HF System. The study populations will be adults (≥18 of age) with New York Heart Association (NYHA) Class III Heart Failure (HF) who have experienced a heart failure hospitalization within the past 12 months.

   The primary safety objectives are evaluate (1) if device/system-related complication (DSRC)-free proportion of subjects is at least 80% at 24 months, and (2) if the pressure sensor failure-free proportion of subjects is at least 90% at 24 months. DSRCs include adverse events related to the systems and is at least treated by invasive means or results in subject death or device explantation.

   The primary effectiveness objective is to demonstrate that there is not a worsening in heart failure (HF) hospitalization rate 1 year in the PAS compared to 1 year prior to enrollment (based on hospitalization records). Effectiveness will be examined

overall, by community and academic hospitals for the training evaluation, and by the following subgroups: women vs. men, reduced ejection fraction (≤ 40%) vs. preserved ejection fraction (> 40%), ischemic vs. non-ischemic etiology, and with ICD/CRT-D vs. without ICD/CRT-D.

Additional objectives will be to analyze 1-year mortality, compare the annualized HF hospitalization or death rate at 1 year in study to the HF hospitalization rate in the year prior to enrollment, and patient compliance.

Patients will be followed out to 2-years post implant with follow-up visits at 1 month and every 6 months. For the two-year primary safety endpoint of freedom from device-related complications, a total of 1,200 subjects will be enrolled, using an exact two-sided test for one-sample binomial proportions with alpha of 0.05, and attrition rate of 49.1%, a minimum of 663 evaluable subjects at 2 years are needed to provide greater than 90% power to detect a difference as small as 5% from the null proportion rate of 0.80 (i.e., objective performance criterion of 80%). Of the enrolled subjects, a total of 420 will be women to ensure a minimum of 206 evaluable women at 2 years to provide greater than 90% power to detect a difference as small as 0.06 from the null proportion rate of 0.90.

2. *Champion Substudy:* This will be a prospective, multi-center, open-label trial conducted in the United States to examine safety and compare the postmarket effectiveness of CardioMEMS™ HF System to premarket. The substudy patients will be all patients selected by independent committee from the PAS 1 (Main Cohort) who are optimally managed and are clinically similar to the Control group in CHAMPION based on pre-enrollment data.

   The primary safety objectives are evaluate (1) if device/system-related complication (DSRC)-free proportion of subjects is at least 80% at 24 months, and (2) if the pressure sensor failure-free proportion of subjects is at least 90% at 24 months. DSRCs include adverse events related to the systems and is at least treated by invasive means or results in subject death or device explantation.

   The primary effectiveness objective is to demonstrate that there is not a worsening in heart failure (HF) hospitalization rate 1 year in the PAS compared to the 1 year HF hospitalization rate in the premarket control group (Part 1). Effectiveness will be examined overall, by community and academic hospitals for the training evaluation, and by the following subgroups: women vs. men, reduced ejection fraction (≤ 40%) vs. preserved ejection fraction (> 40%), ischemic vs. non-ischemic etiology, and with ICD/CRT-D vs. without ICD/CRT-D.

   Patients will be followed out to 2-years post implant with follow-up visits at 1 month and every 6 months. Using an exact one-sample, 2-sided Poisson 95% confidence interval with alpha of 0.05, and a 2 year attrition rate of 49.1%, a minimum of 256 evaluable patients are required to achieve 90% power to show a difference between the estimated Treatment rate of 0.52 and the control rate of 0.75 for effectiveness.

The applicant's manufacturing facility has been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XV. References

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