The CardioMEMS *Champion*™ HF Monitoring System for Patients with NYHA Class III Heart Failure

Summary of Safety and Effectiveness for the Circulatory Systems Device Panel Advisory Committee

December 8, 2011

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1. General Information

Device generic name: CardioMEMS Heart Failure Monitoring System

Device trade name: Champion™ HF Monitoring System

Applicant's name and address: CardioMEMS, Inc.
387 Technology Circle, NW, Suite 500
Atlanta, Georgia 30313

PMA number: P100045

2. Proposed Indication for Use

The Champion HF Monitoring System is indicated for wirelessly measuring and monitoring 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 to reduce heart failure hospitalizations.

The Champion HF Monitoring System is used by the physician in the hospital or office setting to obtain and review PA Pressure Measurements. The Champion HF Monitoring System is used by the patient in the home or other remote location to wirelessly obtain and send hemodynamic and PA pressure measurements to a secure database for review and evaluation by the patient's physician.

3. Device Description

The Champion™ HF Monitoring System (System) provides Pulmonary Artery (PA) hemodynamic data using a wireless Sensor. PA hemodynamic monitoring is used in the management of heart failure (HF). Changes in PA pressure can be used along with heart failure signs and symptoms to adjust medications. The System utilizes radiofrequency (RF) energy to power the Sensor and to measure PA pressure. The System consists of 3 components:

1. Implantable Sensor/Monitor with Delivery Catheter
2. Patient Electronics System or Hospital Electronics System
3. Patient Database

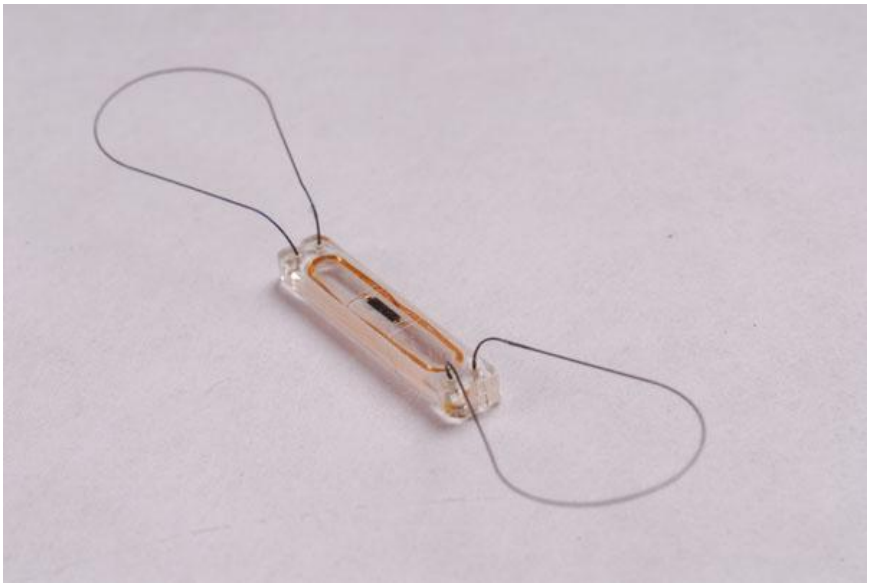
The System provides the physician with the patient's PA pressure waveform including systolic, diastolic, and mean pressures as well as heart rate. The Sensor is permanently implanted into the distal PA using transcatheter techniques in the catheterization laboratory where it is calibrated using a Swan Ganz catheter. PA hemodynamic measurements are taken by the patient at home in a supine position on a padded antenna and pushing one button which records an 18 second continuous waveform. The data can be recorded from the home, hospital, physician's office or clinic.

The hemodynamic data, including a detailed waveform, is transmitted to a secure website that serves as the Patient Database so that PA Monitoring is available to the physician or nurse at any time via the internet.

3.1 Implantable Sensor/Monitor

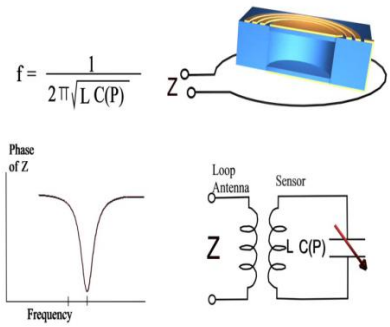
The Sensor is implanted in a branch of the left or right pulmonary artery via a transvenous catheter. The dimensions of the sensor are 15mm in length, 3.4mm in width and 2mm thick (Figure 1). The Sensor remains in the pulmonary artery as a permanent implant.

Figure 1. Implantable Sensor/Monitor



The Sensor is a high-Q LC resonant circuit. The capacitance of the sensor is a function of the pressure in the sensor's environment. The resonant frequency of the sensor is a function of the capacitance and is measured by the electronics unit.

Figure 2. Electrical Schematic of Sensor



Because of the presence of the coil (inductor), the Sensor can be electro-magnetically coupled and the resonant frequency of the LC circuit can be measured remotely. This allows for wireless communication with the Sensor and eliminates the need for on-board source of energy, such as a battery. As a result, the location of the Sensor within a distal pulmonary artery branch allows for measuring the pressure within the artery in a simple, noninvasive procedure by remotely interrogating the Sensor, recording the resonant frequency and converting this value to a pressure measurement (Figure 2).

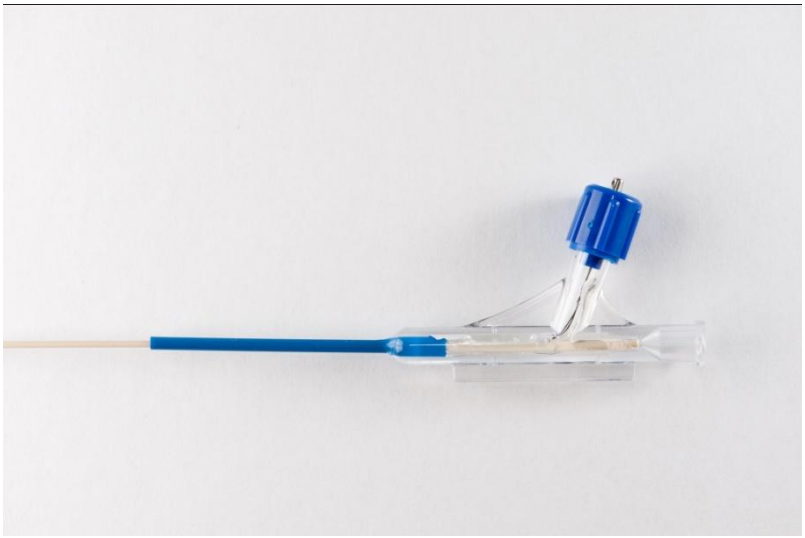
3.2 Implantable Sensor/Monitor Delivery System

The Sensor is tethered to an over-the-wire delivery catheter to create the Delivery System. The Implantable Sensor/Monitor Delivery System includes a hydrophilic coating on the distal portion of the catheter shaft. The usable length is 120cm and it is compatible with a 0.018" guidewire. A RHC is performed and the 0.018" guidewire is advanced through the Swan-Ganz catheter into the distal pulmonary artery. The Swan-Ganz catheter is removed and the Delivery System is advanced 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. The Delivery System is then removed.

Pictures of the Delivery System (distal and proximal sections) are provided in Figure 3 and Figure 4 below.

Figure 3. Distal section of the Implantable Sensor/Monitor Delivery System

Figure 4. Proximal section of the Implantable Sensor/Monitor Delivery System



3.3 Electronics Unit

The Champion Electronics System consists of the following components:

1. Hospital Unit
2. Home Unit
3. Antenna

The Electronics use an antenna to transmit pulses of RF energy to the Sensor. During the RF pulse, the Sensor accumulates energy and after the excitation stops, the energy is re-radiated by the Sensor and received by the Electronics unit. The pressure information is encoded in the frequency of the Sensor transmit signal.

The antenna is connected to the Electronics Unit and is used to interrogate the sensor. The antenna may be either rigid (Hospital System –Figure 5) or flexible (Home System –Figure 6 and Figure 7). The Hospital and Home Systems are identical except for greater functionality in the Hospital System including display of the pressure data which is not available on the Home System.

Figure 5. Rigid antenna assembly

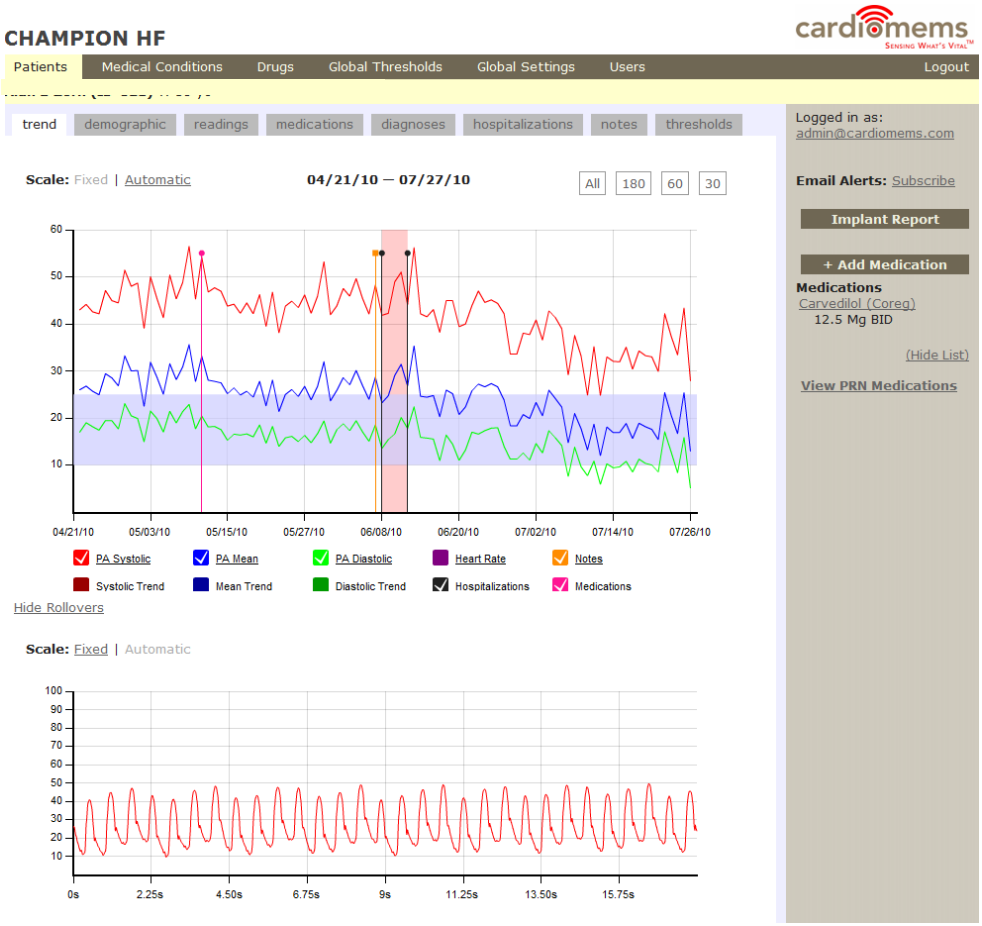
Figure 6. Flexible antenna assembly

Figure 7. Flexible antenna assembly in patient pillow

3.4 Champion HF Website

The Champion HF Website provides a secure user interface for the clinician to review the pulmonary artery pressure data from the HF Pressure Measurement System (Figure 8).

Figure 8. Champion HF Website



4. Clinical Considerations

Who Should Receive the Champion HF Monitoring System

Patients eligible to receive and use the Champion HF Monitoring System are as follows:

- Male or female, at least 18 years of age
- Diagnosis of HF ≥ 3 months, with either preserved or reduced LVEF
- Diagnosis of NYHA Class III HF
- Patients taking a beta blocker for 3 months and an ACE-I or ARB for one month unless the subject is intolerant to beta blockers, ACE-I or ARB.
- Patients with a minimum of one HF hospitalization within past 12 months
- Patients with pulmonary artery branch diameter sized between 7mm and 15mm (implanted vessel)
- Patients with Cardiac Resynchronization Device (CRT) implanted after 3 months

Who Should Not Receive the Champion HF Monitoring System

Patients who are not eligible to receive and use the Champion HF Monitoring System are as follows:

- Patients with an active infection
- Patients with a history of recurrent (> 1) pulmonary embolism or deep vein thrombosis
- Patients unable to tolerate a right heart catheterization
- Patients who have had a major cardiovascular event (e.g., myocardial infarction, stroke) within 2 months of Initial Assessment
- Patients with a Glomerular Filtration Rate (GFR) <25 ml/min who are non-responsive to diuretic therapy or who are on chronic renal dialysis
- Patients with congenital heart disease or mechanical right heart valve(s)
- Patients with a hypersensitivity or allergy to aspirin, and/or clopidogrel

5. Contraindications, Warnings, and Precautions

Contraindications

Inability to take dual antiplatelet or anticoagulants for one month post implant.

Clinical Warnings and Precautions

Sensor/Monitor and Delivery System

The implant procedure must be performed under fluoroscopic guidance.

The patient's PA vessel inner diameter must be > 7mm at the site of device implant. Following device implantation, all subsequent right heart catheterizations must be performed under fluoroscopic guidance. Without fluoroscopy, there could be inadvertent entanglement of the Swan-Ganz catheter with the device.

Follow standard procedure for catheterization of patients receiving anti-coagulation therapy. An INR of <1.5 is recommended prior to RHC and implant if on anticoagulant therapy.

If the distance between the external posterior surface of the patient's thorax and the target implant site is > 10cm, there could be increased difficulty acquiring the Sensor signal. If the patient's BMI is greater than 35, measure the patient's chest circumference. If the chest circumference is > 65 in, Sensor implantation should not occur.

Patients who are currently on chronic anticoagulant therapy should restart treatment after pressure Sensor implantation. Patients who are not currently being treated with chronic anticoagulant therapy should be placed on aspirin (81 mg or 325 mg) and clopidogrel (75 mg) daily for one month following the Sensor implant procedure. After one month, the patient should continue aspirin therapy.

For patients at risk for gastro-intestinal bleeding during the period in which dual antiplatelet therapy is given, the investigator should consider a proton pump inhibitor. Subjects at risk include the elderly; those with a history of gastroduodenal ulcers, GERD, esophagitis, intestinal polyps or cancer. Subjects who smoke or who are using steroids or non-steroidal anti-inflammatory drugs may also be at risk.

6. Alternative Practices and Procedures

Pulmonary artery pressure is currently measured through a right heart catheterization (RHC) procedure, that is, a procedure where 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, indiscriminate use of the procedure to obtain pulmonary artery pressure over an extended time period is impractical and associated with significant risks. Such related risks include bruising and/or bleeding at the insertion site, trauma to the vein, trauma to the heart and lung puncture (if the neck or chest veins are used). Other inherent risks include the presence 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. In order to minimize the potential risks associated with repeated RHC's and target HF therapy to the medical condition of the patient, a non-invasive measurement of pulmonary artery pressures which can be used in either the hospital or home environment is needed.

7. Regulatory and Marketing History

Working in consultation with FDA, CardioMEMS developed the clinical study design for the Champion HF Monitoring System. Enrollment in the randomized study began in September 2007. The clinical study completed enrollment in October 2009 and the clinical module for the PMA was submitted to FDA in December 2010.

The Champion HF Monitoring System received CE certification in November 2010.

No products have been marketed or withdrawn from the market in any country.

8. Summary of Preclinical Studies

a. Laboratory studies

Extensive non-clinical laboratory studies were performed on the Sensor, Delivery System, and Electronics.

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

Sensor	
Simulated Use Cycle Testing	This testing showed the Sensor continued to function per specification throughout 10 years of simulated fatigue testing (400 million cycles).
Temperature Sensitivity	-1mmHg/degree C.
Over-Pressure Evaluation	The Sensors showed no effect from over pressurization.
Mechanical Shock Testing	Sensor performance was not altered by mechanical shock.
Sensor Accuracy Testing	This testing demonstrated that each Sensor meets accuracy and other critical functional performance requirements prior to acceptance for use. The HF sensor accuracy requirements for the application are +/- 2 mmHg at baseline pressure and +/- 3% across the dynamic range.
Sensor Distance Testing	This testing measured the maximum acquisition distance of a Sensor in a simulated use test method. The average distance at 50% signal strength was 5.35 inches, which meets the acquisition distance specification of >4.0 inches for the heart failure application.
Corrosion Testing	This testing confirmed that the Nitinol wire used for the device is corrosion resistant.
MRI Compatibility Testing	This testing determined that there were no effects of a 1.5- and 3-Tesla MRI System on 1) imaging artifacts near the Sensor, 2) tissue heating in areas around the Sensor, 3) Sensor migration and 4) Sensor function.
Defibrillator Compatibility	This test determined that is the Sensor was exposed to an external defibrillator it would cause no patient safety concerns and would not impact Sensor function.
Ultrasound Compatibility	This testing showed that there was no effect of ultrasonic imaging on the function of the Sensor.
Pacemaker and ICD Compatibility	The *Champion* HF Monitoring System did not affect these devices.
Delivery System with Sensor	
Design Verification Testing	This testing verified that the HF Delivery System design met the acceptance criteria for 1) removal of the catheter from the packaging, 2) catheter preparation, 3) advancement of the catheter over the guidewire, 4) loading of the catheter into the venous sheath, 5) positioning the Sensor in the pulmonary artery, 6) retraction into the sheath, 7) Sensor attachment, 8) Sensor visual inspection post-delivery, 9) catheter integrity post-removal and 10) wire loop integrity post-removal. Catheter shaft tensile strength was also satisfactory.
Ship and Environmental Testing	Ship Testing demonstrated that the packaged Delivery System with Sensor met ISTA-2A ship test and environmental conditioning requirements.
Packaging and Label Visual	This testing demonstrated that there was no damage to inner pouch assembly and that the hoop assembly remained intact. It also showed that

Inspection	all labeling remains legible.
Pouch Bubble Emission Test	This testing demonstrated that the pouch remained sealed and the sterile barrier was not compromised.
Pouch Seal Tensile Test	This testing demonstrated that the pouch seal strength was adequate.
Hydrophilic Coating Testing	This testing verified that the hydrophilic coating met the performance criteria for coating friction/durability and integrity.
Radiopacity Testing	This testing evaluated the concentration of barium sulfate added to the delivery catheter to enhance visibility during Sensor implant. The delivery system was easily able to be seen under radiographic imaging.
Shelf-life Testing	Accelerated and real-time aging of the device and packaging was performed and established a 2-year shelf life.
Biocompatibility Testing	See Table 2.
Electronics Unit	
Electrical Safety Testing	The test results indicate that the electronics unit with antenna complied with the requirements presented within UL 60601-1 and IEC 60601-1.
Electromagnetic Compatibility Testing	The test results indicate that the electronics unit with antenna complied with the requirements presented within IEC/EN 60601-1-2:2001, Medical Electrical Equipment – Electromagnetic Compatibility, ETSI/EN 301 489-1 V1.6.1 (2005-09), Electromagnetic Compatibility (EMC) standard for radio equipment and services; Part 1: Common technical requirements, ETSI EN 301 489-3 V1.4.1 (2002-08), Specifications for Short-Range Device (9 kHz to 40 GHz). IEC/EN 60601-1-2, ETSI/EN 301 489-1 and ETSI EN 301 489-3.
Emissions Testing	The test results indicate that the electronics unit with antenna complied with the requirements presented within EN 302 510-1 V1.1.1 (2007-04) + EN 302 510-2 V1.1.1 (2007-04), Radio equipment in the frequency range 30 – 37.5MHz for ultra low power active medical implants and accessories, EN 60601-1-2:2001, Medical Electrical Equipment – Electromagnetic Compatibility, and EN 55022:1998, Information technology equipment - Radio disturbance characteristics- Limits and methods of measurement EN 302 510-1 + EN 302 510-2, EN 60601-1-2 and EN 55022.
FCC Testing	The Sensor was granted Part 15 authorization under FCC identifier R3PCS-A-00051. Additional electromagnetic compatibility FCC Part 18 testing was performed in accordance with the requirements specified within the following document: FCC Parts18 & 2 (ET Docket 95-58) and ICES-003 (Issue 4 June 2006), Industrial, Scientific and Medical Equipment. The test results indicate that the electronics unit with antenna complied with the requirements presented within the above FCC reference document.
Design Testing	Design verification testing was performed on the Electronics system, including the sensor, antenna, main unit and the associated software, to ensure that essential input requirements were met. The requirements included accuracy, distance, noise, frequency range, and ease of use. All

	units passed the testing.
Thermal Assessment Test	This testing demonstrated that the cooling characteristics of the Electronics Unit were adequate to ensure correct functionality.
Flexible Antenna and Pad Set Verification Testing	This testing demonstrated that the flexible antenna and pad set met all of electrical testing, environmental testing, and mechanical testing which included simulated cycle testing, peel testing, strain relief testing, cover junction testing, durability testing and drop testing set forth in the design requirements.
Mechanical Testing	Mechanical characteristics of the Electronics Unit, rigid antenna and flexible antenna, were tested to ensure that general safety and flammability requirements were met. These requirements are those set forth in UL-60601-1 and UL-94. All units passed and the requirements were met.
Label Durability Testing	Testing showed that the labels met the integrity and legibility of the text standards. Labels were also tested to demonstrate indelibility of the ink.
Ship and Environmental Testing	Ship Testing demonstrated that the Electronics met ISTA-2A ship test and environmental conditioning requirements (environmental conditioning, vehicle stacking, vibration and drop testing).

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 Testing

Test Performed	Test Method	Results
Cytotoxicity	ISO Elution Method (1xMEM Extract)	No evidence of cell lysis or toxicity. Test requirements were met.
Sensitization	ISO Maximization Sensitization Study (Extract)	No evidence of delayed dermal contact sensitization.
Intracutaneous Reactivity	ISO Intracutaneous Study (Extract)	Each test extract article met the requirements of the test.
Acute Systemic Toxicity	ISO Systemic Toxicity Study (Extract)	No mortality or evidence of systemic toxicity.
Hemolysis	ASTM Hemolysis	Each test extract article met the requirements of the test.
C3a Complement Activation	C3a Complement Activation Assay	Not considered to be an activator of the complement system.
SC5b-9 Complement Activation Assay	SC5b-9 Complement Activation Assay	Each test extract article met the requirements of the test.
USP Pyrogen Study	USP Pyrogen Study (Material Mediated)	Non-pyrogenic
Chromosomal Aberration	In vivo Chromosomal Aberration Study in Mammalian Cells (extract)	Non-genotoxic
Bacterial Reverse Mutation	Bacterial Reverse Mutation Study (Saline Extract and DMSO Extract)	Considered non-mutagenic in both extracts
Mouse Micronucleus	Mouse Bone Marrow Micronucleus Study	Non-genotoxic
Muscle Implantation	ISO Muscle Implantation Study	Macroscopic reaction was not significant.
Carcinogenicity	Carcinogenicity Testing	Testing not performed. Justification provided for no risk of carcinogenesis associated with clinical use.

Test Performed	Test Method	Results
Chronic Toxicity and Histopathology	Porcine animal model	The chronic toxicity testing showed tissue responses in these studies were comparable to other vascular implants. The histopathology analysis showed that the sensors were well tolerated by the local pulmonary arterial wall and incorporated into the pulmonary artery tissue by stable fibrocellular encapsulation.
Particulate Testing	USP 788 Particulate Testing	Met particulate requirement of the standard.

Numerous engineering bench and simulated studies were performed during the development of the HF System (Table 3). As such, the Champion HF Monitoring System conforms to the following US and International Standards:

Table 3. US and International Standards

Standard	Title
EN ISO 11607	Packaging for terminally sterilized medical devices
EN 45502	Active Implantable Medical Devices, General Requirements
ISTA 2A	International Safe Transit Association Medical Package Testing
EN ISO 11135	Sterilization of health care products - Ethylene oxide
EN ISO 10993	Biological evaluation of medical devices
EN ISO 10555	Sterile, single-use intravascular catheters - General requirements
ASTM F2052-02, F2182-02a, F2213-04, F2119-01	MRI Compatibility
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
EN 60601-1	Medical Electrical Equipment

EN 302 510	Electromagnetic compatibility
EN 55022	Radiated emissions
EN 62304	Life Cycle Requirements for Medical Device Software

b. Animal studies

Chronic GLP studies were performed in 9 miniature pigs that were implanted 2 Sensors in each animal with follow-up periods of 3, 6, and 12 months; three pigs per grouping. Hemodynamic, gross, and histologic outcomes were compared between CardioMEMS to the use of conventional Swan Ganz catheters. There was no mortality. The devices performed as intended. Due to slight over sizing in the swine model compared to the human, there was one incidence of a partial thrombus in the pulmonary artery of one pig. Otherwise there was generally good biologic response and the sensors were fully endothelialized and generally well tolerated. Readings were obtained from all sensors throughout the studies.

9. Feasibility Studies

Three feasibility studies comprising 55 patients were conducted in Brazil, Chile, Germany, and the United States. The objective of these studies was to evaluate the performance of the HF Sensor/Monitor and the incidence of adverse events post implant procedure. Table 4 provides a summary of general information for each study.

Table 4. Feasibility Studies General Information

Study #	Patients Enrolled (#)	Study Sites (#)	Country	Study Start – Completion	Implant Technical Success Rate (%)
CM-05-04	28	3	Chile and Brazil	12/05 – 4/07	89
CM-06-05	10	1	Germany	10/06 – 9/08	90
CM-06-03	17	5	United States	12/06 – 8/07	100

Safety was monitored by collection and evaluation of the occurrence of anticipated and unanticipated adverse events during the study. The evaluation of safety data demonstrated that the Pressure Sensor can be safely implanted by an endovascular delivery catheter into the distal pulmonary artery. Adverse events were minimal and resolved without sequelae.

Sensor performance was assessed in all studies by comparison of pulmonary artery pressure (PAP) between the Sensor and a Swan-Ganz (SG) catheter during follow-up measurements. Comparisons were performed at 60 days post implant in all feasibility studies, and at 6 month, 1 year, and 2 year in the CM-05-04 study. The data from the 60 day follow-up from all feasibility studies are presented in Table 5. The comparisons for the later time points are presented in Table 6, Table 7 and Table 8.

Table 5. Pulmonary Artery Pressures by Sensor and Swan-Ganz at 60 Days Follow-up

Pulmonary Artery Pressure Parameter	Comparison Sample Size (n)	Sensor (mm Hg)		Swan-Ganz (SG) (mm Hg)		Sensor – SG Difference (mm Hg)		Pearson Correlation Coefficient (r)
		Mean	SD	Mean	SD	Mean	SD	
Systolic	43	47	20	51	17	-4	9	0.89
Diastolic		22	12	22	10	0	9	0.70
Mean		32	15	33	12	-1	8	0.83

Table 6. Pulmonary Artery Systolic Pressure by Sensor and Swan-Ganz (SG) Catheter

Follow-Up Timepoint	Comparison Sample Size (#)	Sensor (mm Hg)		SG Catheter (mm Hg)		Sensor – SG Difference (mm Hg)		Pearson Correlation Coefficient (r)
		Mean	SD	Mean	SD	Mean	SD	
6 month	8	57	18	55	21	1	5	0.98
Year 1	13	48	18	52	19	-5	8	0.91
Year 2	9	59	23	63	26	-5	9	0.94

Table 7. Pulmonary Artery Diastolic Pressure by Sensor and Swan-Ganz (SG) Catheter

Follow-Up Timepoint	Comparison Sample Size (#)	Sensor (mm Hg)		SG Catheter (mm Hg)		Sensor – SG Difference (mm Hg)		Pearson Correlation Coefficient (r)
		Mean	SD	Mean	SD	Mean	SD	
6 month	8	23	10	25	8	-2	5	0.85
Year 1	13	22	14	25	10	-3	7	0.86
Year 2	9	31	17	29	11	2	10	0.80

Table 8. Pulmonary Artery Mean Pressure by Sensor and Swan-Ganz (SG) Catheter

Follow-Up Timepoint	Comparison Sample Size (#)	Sensor (mm Hg)		SG Catheter (mm Hg)		Sensor – SG Difference (mm Hg)		Pearson Correlation Coefficient (r)
		Mean	SD	Mean	SD	Mean	SD	
6 month	8	37	13	37	13	0	3	0.97
Year 1	13	32	16	35	13	-3	7	0.91
Year 2	9	43	19	42	16	1	7	0.93

The follow-up comparisons showed good correlation between the Sensor and Swan-Ganz measurements at all follow-up time points.

The results observed during the feasibility studies provided a basis for proceeding to the CHAMPION Clinical Study. These data and results for the feasibility studies have been previously submitted to the Food and Drug Administration (FDA) as part of the

investigational device exemption (IDE) application (IDE G060187/S006) and annual reports (2008 IDE G060187/S037, 2009 IDE G060187/S048).

10. Trial - CHAMPION Clinical Trial

10.1 Study Objectives and Endpoints

Study Objective

The objective of the study was to evaluate the safety and efficacy of the HF Pressure Monitoring System (now named the Champion HF Monitoring System) in reducing HF hospitalizations in a subset of subjects suffering from HF.

Primary Endpoints

Primary Safety Endpoints

The primary safety endpoints were 1) Rate of Device / System-related Complications (DSRC), and 2) Rate of Pressure Sensor Failures.

Primary Efficacy Endpoint

Primary efficacy was measured by the rate of HF hospitalizations at 6 months.

Secondary Endpoints

The secondary efficacy variables and their hierarchical order of testing (for multiplicity control) were as follows:

1. Change from baseline in pulmonary artery pressures
2. Proportion of subjects hospitalized for heart failure
3. Days alive outside of the hospital
4. Quality of Life -Minnesota Living with Heart Failure Questionnaire (MLHFQ)

Additional Analyses

1. DSRCs and Sensor Failures after 6-month follow-up Visit
2. HF hospitalizations over Study Duration
3. Secondary Efficacy Analysis over Study Duration
4. HF hospitalizations with Covariates over the Study Duration
5. All Cause Hospitalizations
6. Frequency of HF Hospitalizations
7. HF Medication Results
8. Baseline EF

9. Survival Analysis
10. HF Hospitalization Free Survival
11. Screening and 6-month Creatinine

Survival Analysis

Subject survival rates were measured from the Baseline visit to the date of death, on or before 6 months post-randomization, or censored at last date known alive, on or before 6 months post randomization.

10.2 Study Hypotheses

Primary Safety Hypotheses

The primary safety endpoints were tested hierarchically, in order to control for multiplicity. Employing the O'Brien Fleming analysis methodology for one 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 months was at least 80%. The statistical hypotheses were:

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

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

Primary Efficacy Hypothesis

Employing the O'Brien Fleming analysis methodology for one 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 Champion HF Monitoring 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 hospitalizations through 6 months.

Event Definitions

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 of the following: a) 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), b) results in the death of the subject, or c) results in the explant of the device.

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.

A HF Hospitalization was defined by the CEC as a hospitalization in which the patient must be admitted for heart failure or heart failure must be the primary reason for admission. Criteria must include both of the following:

A. Signs and symptoms of heart failure on admission,
B. The use of intravenous diuretic, vasodilator, inotropic, or ultrafiltration therapy for the purposes of treating heart failure. The augmentation of oral therapy may be allowable for defining the admission as heart failure, if no other reasonable diagnosis can be attributed to the admission.

10.3 Investigational Plan and Methods

Study Design

This was a prospective, randomized, single-blind, multi-center, trial enrolling 550 patients at 64 sites in the US. Patients were required to have been diagnosed with HF for at least 3 months and be NHYA Class III at time of enrollment. In contrast to most other trials of heart failure devices, patients with preserved or reduced ejection fraction were eligible. The reduced ejection fraction patients were required to be on stable AHA/ACC guidelines based medical therapy. Patients were also required to have been hospitalized for HF at least once in the preceding 12 months. Key exclusion criteria included: recurrent pulmonary emboli or deep venous thromboses; CRT implantation within the preceding 3 months; and glomerular filtration rate (GFR) <25 ml/min. Subjects meeting the inclusion/exclusion criteria were randomized to the treatment or control groups following the sensor implant but prior to hospital discharge.

Following the sensor implant procedure, subjects were hospitalized overnight for observation. Prior to hospital discharge, all subjects were trained on how to operate the home electronic monitoring unit and instructed to take his/her pulmonary artery pressure measurements daily. All patients took daily pressure readings regardless of randomization assignment. These measurements were transmitted via modem to a secure patient database. Patients were kept blinded to treatment assignment until the last patient in the trial completed their 6 month follow-up visit.

In the treatment group, investigators provided standard of care HF management plus HF management based on hemodynamic information obtained from the Champion database. In the control group, investigators provided standard of care HF management but did not have access to patient hemodynamic data. The single-blind was maintained until analysis of the 6-month data was complete for the entire patient population, at which point, the investigators had access to all subjects' data at their site.

The institutional review board of each participating center approved the study protocol, and all patients signed an informed consent. An independent Data Safety Monitoring Board (DSMB) reviewed all available safety and efficacy data. In addition, the DSMB conducted an unblinded interim analysis after 50% of the patients completed at least 6 months of follow-up to allow the DSMB to make recommendations related to the safety and efficacy of the CHAMPION trial. An independent, blinded, Clinical Events Classification Committee (CEC) reviewed all available clinical data and determined when HF hospitalization endpoints

were met. All adverse events, hospitalizations, and deaths were reviewed and adjudicated by the CEC and used in the final efficacy and safety analyses.

Study Scope and Duration

Follow-up study visits for both the treatment and control groups were scheduled at Month 1, Month 3, Month 6, and every 6 months thereafter. Follow-up visits included a physical exam, evaluation of NYHA Class, adverse event assessment and medication review. Subjects will be followed for long-term safety for three years after enrollment or until PMA approval.

Enrollment Methodology

All potential study subjects who met the protocol specified inclusion criteria and none of the exclusion criteria were eligible for the study.

Randomization Methods

Randomization was used to avoid bias in the assignment of subjects to the group (treatment or control), to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) were evenly balanced across randomized groups, and to enhance the validity of statistical comparisons across treatment groups.

Subjects were randomized (treatment or control) following the RHC and sensor implant but prior to hospital discharge. Randomization was performed after the RHC and sensor implant in order to minimize any bias regarding the decision to implant the sensor based on the hemodynamic data obtained from the RHC.

The randomization was balanced by using randomly permuted blocks and study center; randomization was performed in a 1:1 ratio based on a computer-generated randomization schedule prepared before the start of the study. An interactive system was used to assign subjects to a randomized group and to document the randomization assignment.

Treatment Group

The investigator provided standard of care HF management plus HF management based on hemodynamic information obtained from the Champion HF Monitoring System. The investigator or designee reviewed the PA pressure measurements transmitted to the database

from the home monitoring unit. Default alert limits were set at the normal pulmonary artery pressures (Table 9) and were customizable at the investigator's discretion.

Table 9. Normal Pulmonary Artery Pressures

PA Measure	Pressure Ranges
PA Systolic	15 - 35 mmHg
PA Diastolic	8 - 20 mmHg
PA Mean	10 - 25 mmHg

The Investigator or designee reviewed the HF pressure measurements at least weekly. The Investigator or designee made medication changes to manage pulmonary artery pressure according to the recommendations in the study protocol.

Control Group

The investigator provided standard of care HF management. All patients in the control group were implanted with the sensor and took home readings. Although the patients transmitted pressure readings to the central location, the investigator did not have access to the daily home pulmonary artery pressure measurements until all patients had completed their 6-month follow-up.

Follow-up Visits

Follow-up visits and evaluations were performed based on the schedule of events provided in Table 10 below.

Table 10. 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 (incl. weight)	X[1]	X(Abbreviated PE)[3]	X[3]	X[3]	X[3]	X[3]
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

Study Objective

The objective of the study was to evaluate the safety and efficacy of the HF Pressure Measurement System in reducing heart failure hospitalizations in a subset of subjects suffering from HF.

Study Design

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 groups:

- TREATMENT group: standard of care HF management plus HF management based upon hemodynamic information obtained from the HF Pressure Measurement 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 Pressure Measurement 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 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.

Study Inclusion Criteria

The list of inclusion criteria was as follows:

1. Written informed consent obtained from subject or legal representative.
2. Male or female, at least 18 years of age
3. Diagnosis of HF ≥ 3 months, with either preserved or reduced LVEF
4. Diagnosis of NYHA Class III HF (historical assessment documented at screening visit)
5. At least one HF hospitalization within 12 months of Screening Visit
6. Subjects with reduced LVEF must be receiving a beta blocker for three months and an ACE-I or ARB for one 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 month prior to study entry.
7. 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.
8. Subjects with implant pulmonary artery branch diameter between 7mm and 15mm.
9. 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 years, has had a total hysterectomy, or has had a bilateral tubal ligation.
10. Subjects willing and able to comply with the follow up requirements of the study.

Study Exclusion Criteria

The list of exclusion criteria was as follows:

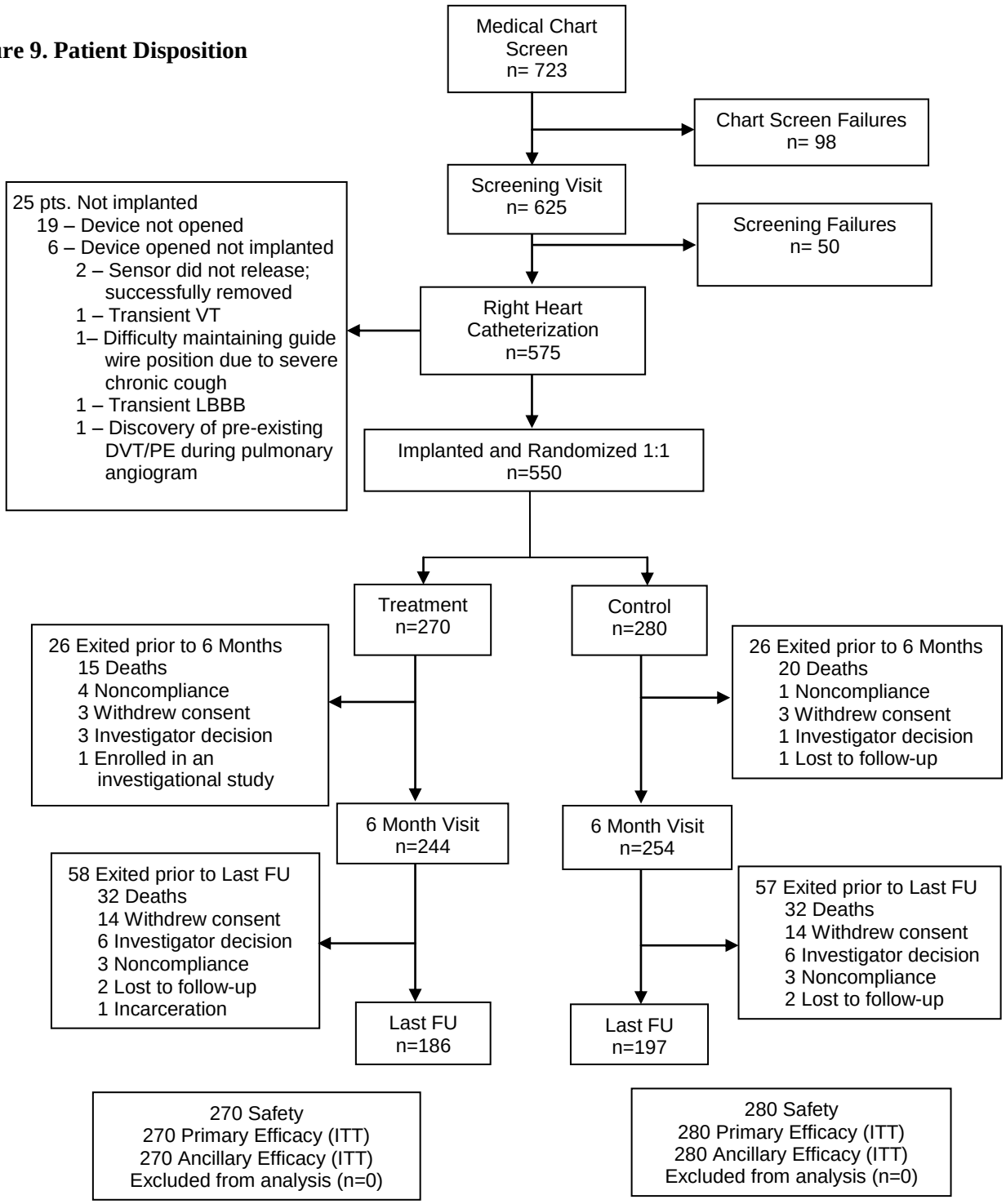
1. Subjects with an active infection.
2. Subjects with history of recurrent (> 1) pulmonary embolism or deep vein thrombosis.
3. Subjects, in the Investigator's opinion, unable to tolerate a right heart catheterization.
4. Subjects who have had a major cardiovascular event (e.g., myocardial infarction, stroke) within two months of Screening Visit.
5. Subjects with Cardiac Resynchronization Device (CRT) implanted ≤ 3 months prior to enrollment.
6. Subjects with a Glomerular Filtration Rate (GFR) <25 ml/min who are non-responsive to diuretic therapy or who are on chronic renal dialysis.
7. Subjects likely to undergo heart transplantation within six months of Screening Visit.

8. Subjects with congenital heart disease or mechanical right heart valve(s).
9. Subjects with known coagulation disorders.
10. Subjects with a hypersensitivity or allergy to aspirin, and/or clopidogrel.
11. Subjects enrolled in concurrent studies that may confound the results of this study.
12. Subjects whose clinical condition, in the Investigator's opinion, would not allow them to complete the study.

10.4 Patient Disposition

A total of 723 patients were screened for study eligibility (Figure 9).

Figure 9. Patient Disposition



A total of 575 patients were consented and transferred to the cath lab for sensor implant. However, 25 patients were not enrolled – in 19 patients, the device was not opened due to inability to perform a RHC or patient ineligibility based on angiographic anatomy; in 6 patients, the implant was not completed for the reasons listed above (Figure 9). These 25 patients were followed for 30 days for safety and are included in the primary safety endpoint. Therefore a total of 550 patients were implanted and randomized 1:1 to the treatment group (n=270 patients) or to the control group (n=280 patients).

Six month follow up was completed in 244 of 270 patients in the Treatment group. There were a total of 26 patients who exited the study prior to 6 months, including 15 patients who died and 11 patients who exited the study for noncompliance (n=4), withdrawal of consent (n=3), Investigator decision (n=3) or other reason (n=1). For the Control group, 6 month follow up was completed in 254 of 280 patients. There were a total of 26 patients who exited the study prior to 6 months including 20 deaths and 6 patients who exited the study for withdrawal of consent (n=3), Investigator decision (n=1), lost to follow-up (n=1) or noncompliance (n=1).

Table 11 summarizes patients' duration (days) in the trial. For the primary analysis up to the 6 month visit, patients averaged 176.6 days in the treatment group and 175.9 days in the control group. Over the entire duration of the trial, the average duration was 459.7 days for the treatment group and 450.0 days in the control group.

Table 11. Patient Duration in the Trial

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)
Follow-up Up to 6 Month Visit (days)			
Mean±StdDev (N)	176.6±29.6 (270)	175.9±35.4 (280)	176.3±32.6 (550)
(95% CI)	(173.1 - 180.2)	(171.8 - 180.1)	(173.5 - 179.0)
Total	47,686	49,259	96,945
Follow-up After 6 Month Visit (days)			
Mean±StdDev (N)	313.2±189.3 (244)	302.2±185.3 (254)	307.6±187.2 (498)
(95% CI)	(289.3 - 337.1)	(279.3 - 325.1)	(291.1 - 324.1)
Total	76,422	76,748	153,170
Patient Duration in Study (days)			
Mean±StdDev (N)	459.7±212.4 (270)	450.0±210.6 (280)	454.8±211.3 (550)
(95% CI)	(434.2 - 485.1)	(425.3 - 474.8)	(437.1 - 472.5)
Total	124,108	126,007	250,115

10.5 Screening and Demographic Characteristics

The patient screening and baseline demographic characteristics are provided below in Table 12 and Table 13. In general, patients enrolled in this study were comparable to the majority of clinical trials involving patients with heart failure. The mean age was 61.6 years with a range from 22 to 90. The majority of patients were male (72.5%) and Caucasian (72.9%), although there were 24.5% of patients who were Black, Asian, or American Indian. All patients were NYHA Class III at baseline. Previous cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillator (ICD) devices were present in 35.1% and 33.8% of patients respectively. As indicated previously, this trial was different from many other trials in heart failure because patients with either systolic or diastolic heart failure could be enrolled. Most patients had reduced left ventricular systolic function (78.2%) but 21.7% of patients had heart failure with preserved ventricular function (data not available for one subject). Most patients had heart failure secondary to ischemic heart disease (60.4%) with the remainder due to a variety of non-ischemic etiologies.

Table 12. Screening Demographics and Conditions

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)	p-value
Age (years)				
Mean±StdDev (N)	61.3±13.0 (270)	61.8±12.7 (280)	61.6±12.8 (550)	0.5927
(95% CI)	(59.8 - 62.9)	(60.3 - 63.3)	(60.5 - 62.7)	
Gender				
Male	194 (71.9%)	205 (73.2%)	399 (72.5%)	0.7745
Female	76 (28.1%)	75 (26.8%)	151 (27.5%)	
Race				
White	196 (72.6%)	205 (73.2%)	401 (72.9%)	0.9236[2]
Black (of African Descent)	68 (25.2%)	58 (20.7%)	126 (22.9%)	
Asian	0 (0.0%)	3 (1.1%)	3 (0.5%)	
American Indian or Alaskan Native	3 (1.1%)	3 (1.1%)	6 (1.1%)	
Other	3 (1.1%)	11 (3.9%)	14 (2.5%)	
Ethnicity				
Hispanic	14 (5.2%)	19 (6.8%)	33 (6.0%)	0.4757
Non-Hispanic	256 (94.8%)	261 (93.2%)	517 (94.0%)	
BMI				
Mean±StdDev (N)	30.8±6.5 (270)	31.0±7.3 (280)	30.9±6.9 (550)	0.7459
(95% CI)	(30.0 - 31.6)	(30.2 - 31.9)	(30.3 - 31.5)	
BMI > 35				
Yes	64 (23.7%)	65 (23.2%)	129 (23.5%)	0.9200
No	206 (76.3%)	215 (76.8%)	421 (76.5%)	
Chest Circumference				
< 52	42 (15.6%)	48 (17.1%)	90 (16.4%)	0.3421
>=52 & <=65	22 (8.1%)	17 (6.1%)	39 (7.1%)	
> 65	0 (0.0%)	0 (0.0%)	0 (0.0%)	
NYHA Class				
Class I	0 (0.0%)	0 (0.0%)	0 (0.0%)	N/A
Class II	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Class III	270 (100.0%)	280 (100.0%)	550 (100.0%)	
Class IV	0 (0.0%)	0 (0.0%)	0 (0.0%)	
CRT or CRT-D				
Yes	91 (33.7%)	99 (35.4%)	190 (34.5%)	0.7201
No	179 (66.3%)	181 (64.6%)	360 (65.5%)	
ICD				
Yes	88 (32.6%)	98 (35.0%)	186 (33.8%)	0.5889
No	182 (67.4%)	182 (65.0%)	364 (66.2%)	
CRT-D/ICD Implant Days to Baseline				
Mean±StdDev (N)	867.8±830.7 (179)	844.0±732.9 (197)	855.3±780.0 (376)	0.9531
(95% CI)	(745.3 - 990.4)	(741.0 - 947.0)	(776.2 - 934.4)	
Ejection Fraction [3]				
Preserved (EF>=40%)	62 (23.0%)	57 (20.4%)	119 (21.6%)	0.5343
Reduced (EF<40%)	208 (77.0%)	222 (79.3%)	430 (78.2%)	

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)	p-value
Ischemic Cardiomyopathy				
Yes	158 (58.5%)	174 (62.1%)	332 (60.4%)	0.4327
No	112 (41.5%)	106 (37.9%)	218 (39.6%)	
Qualifying HF Hospitalization Days from Baseline [4]				
Mean±StdDev (N)	121.9±104.9 (270)	119.1±99.5 (280)	120.5±102.1 (550)	0.8309
(95% CI)	(109.4 - 134.5)	(107.4 - 130.8)	(112.0 - 129.1)	
Creatinine (mg/dl)				
Mean±StdDev (N)	1.40±0.47 (270)	1.35±0.42 (280)	1.38±0.44 (550)	0.5560
(95% CI)	(1.34 - 1.45)	(1.31 - 1.40)	(1.34 - 1.41)	
GFR (mL/min/1.73m²)				
Mean±StdDev (N)	60.4±22.5 (270)	61.8±23.2 (280)	61.1±22.9 (550)	0.5638
(95% CI)	(57.7 - 63.1)	(59.0 - 64.5)	(59.2 - 63.0)	

[1] P-value testing Treatment vs. Control obtained from exact Wilcoxon Rank-Sum Test for continuous measures and Fisher's exact test for categorical measures.
[2] Comparison of White versus non-white
[3] EF data available only for 549 subjects
[4] Unknown Day was imputed as the first of the month (01) and unknown month was imputed as January

Additional baseline conditions included a mean BMI of 30.9, mean systolic blood pressure of 122.2 mmHg, mean diastolic blood pressure of 72.2 mmHg, and serum creatinine of 1.38 mg/dl.

All of the baseline conditions and characteristics were similar between the treatment and control groups, indicating an effective randomization process.

Table 13. Baseline Condition

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)	p-value
Weight (lb)				
Mean±StdDev (N)	203.6±48.8 (270)	203.7±49.3 (280)	203.6±49.0 (550)	0.8789
(95% CI)	(197.7 - 209.4)	(197.9 - 209.5)	(199.5 - 207.7)	
Height (lb)				
Mean±StdDev (N)	68.3±4.0 (270)	68.1±4.1 (280)	68.2±4.1 (550)	0.5238
(95% CI)	(67.9 - 68.8)	(67.6 - 68.6)	(67.9 - 68.5)	
Systolic BP (mmHg)				
Mean±StdDev (N)	121.2±22.5 (270)	123.2±21.0 (280)	122.2±21.8 (550)	0.1286
(95% CI)	(118.5 - 123.9)	(120.7 - 125.6)	(120.4 - 124.0)	
Diastolic BP (mmHg)				
Mean±StdDev (N)	72.2±13.1 (270)	72.2±13.1 (280)	72.2±13.1 (550)	0.8931
(95% CI)	(70.6 - 73.8)	(70.6 - 73.7)	(71.1 - 73.3)	
Heart Rate (bpm)				
Mean±StdDev (N)	72.4±12.9 (269)	73.0±12.1 (280)	72.7±12.5 (549)	0.4873
(95% CI)	(70.9 - 74.0)	(71.6 - 74.4)	(71.7 - 73.8)	
Temperature (°F)				
Mean±StdDev (N)	97.6±0.8 (247)	97.6±0.8 (251)	97.6±0.8 (498)	0.4742
(95% CI)	(97.5 - 97.7)	(97.5 - 97.7)	(97.5 - 97.7)	
Respiration Rate (breaths/min)				
Mean±StdDev (N)	18.2±2.6 (260)	18.5±2.9 (267)	18.3±2.7 (527)	0.1711
(95% CI)	(17.8 - 18.5)	(18.1 - 18.8)	(18.1 - 18.6)	
INR (sec)[2]				
Mean±StdDev (N)	1.3±0.4 (125)	1.3±0.3 (146)	1.3±0.3 (271)	0.2913
(95% CI)	(1.3 - 1.4)	(1.2 - 1.3)	(1.3 - 1.4)	

[1] P-value testing Treatment vs. Control obtained from exact Wilcoxon Rank-Sum Test for continuous measures and Fisher's exact test for categorical measures.
[2] INR only required for patients on warfarin

Table 14 summarizes the co-morbidities frequently associated with heart disease occurring in greater than 10% of patients. Coronary artery disease, hypertension and hyperlipidemia were the most common co-morbid conditions, occurring in 69.8%, 77.6% and 76.7% of patients respectively. In addition 28.9% of patients had chronic obstructive pulmonary disease and 19.6% of patients had chronic kidney disease. These common co-morbid conditions observed in HF patients often contribute to symptoms of shortness of breath, congestion and edema leading to uncertainty in diagnosis based purely upon clinical assessment.

Table 14. Co-morbidities Occurring in >10% of Patients

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)
Hypertension	207 (76.7%)	220 (78.6%)	427 (77.6%)
Hyperlipidemia	204 (75.6%)	218 (77.9%)	422 (76.7%)
Coronary Artery Disease	182 (67.4%)	202 (72.1%)	384 (69.8%)
History of Myocardial Infarction	134 (49.6%)	137 (48.9%)	271 (49.3%)
Diabetes Mellitus	130 (48.1%)	139 (49.6%)	269 (48.9%)
Atrial tachycardia Flutter/Fibrillation	120 (44.4%)	135 (48.2%)	255 (46.4%)
Chronic Obstructive Pulmonary Disease	76 (28.1%)	83 (29.6%)	159 (28.9%)
Chronic Kidney Disease	54 (20.0%)	54 (19.3%)	108 (19.6%)
Pulmonary Edema	47 (17.4%)	41 (14.6%)	88 (16.0%)
Cerebrovascular Accident	36 (13.3%)	35 (12.5%)	71 (12.9%)
Hypotension	35 (13.0%)	35 (12.5%)	70 (12.7%)
Peripheral Artery Disease	36 (13.3%)	32 (11.4%)	68 (12.4%)
Cerebrovascular Disease	29 (10.7%)	30 (10.7%)	59 (10.7%)

10.6 Implant Procedural Data and Hemodynamics

Implant Data

Right heart catheterization measurements are summarized in Table 15. The mean pulmonary artery (PA) systolic pressure was 45 ± 15 mmHg, the mean PA diastolic pressure was 19 ± 8 mmHg, the mean PA mean pressure was 29 ± 10 mmHg and the mean pulmonary capillary wedge pressure was 18 ± 8 mmHg. The mean cardiac output was 4.5 ± 1.5 L/min and the Cardiac Index was 2.3 ± 0.7 L/min/m². There were no hemodynamic differences between randomized groups at time of implant.

Table 15. Procedural Data

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)	p-value
PA Systolic Pressure (mmHg)				
Mean±StdDev (N)	44±14.2 (269)	45±15.2 (278)	45±14.7 (547)	0.5323
(95% CI)	(42.5 - 46.0)	(43.6 - 47.2)	(43.6 - 46.1)	
PA Diastolic Pressure (mmHg)				
Mean±StdDev (N)	19±8.6 (267)	19±8.1 (278)	19±8.3 (545)	0.3063
(95% CI)	(17.6 - 19.6)	(18.2 - 20.1)	(18.2 - 19.6)	
PA Mean Pressure (mmHg)				
Mean±StdDev (N)	29±10.0 (269)	30±10.0 (278)	29±10.0 (547)	0.3269
(95% CI)	(27.7 - 30.1)	(28.5 - 30.9)	(28.5 - 30.1)	
PA Wedge Pressure (mmHg)				
Mean±StdDev (N)	18±7.9 (260)	19±8.3 (274)	18±8.1 (534)	0.0840
(95% CI)	(16.8 - 18.8)	(18.0 - 20.0)	(17.7 - 19.1)	
Cardiac Output (L/min)				
Mean±StdDev (N)	4.5±1.4 (268)	4.5±1.5 (277)	4.5±1.5 (545)	0.6647
(95% CI)	(4.3 - 4.7)	(4.4 - 4.7)	(4.4 - 4.6)	
Cardiac Index (L/min/m²)				
Mean±StdDev (N)	2.3±0.6 (268)	2.3±0.7 (277)	2.3±0.7 (545)	0.5536
(95% CI)	(2.2 - 2.4)	(2.2 - 2.4)	(2.3 - 2.4)	

[1] P-value testing Treatment vs. Control obtained from exact Wilcoxon Rank-Sum Test for continuous measures and Fisher's exact test for categorical measures.

The total procedure time for both groups averaged 54.3 ±31.6 minutes from skin to skin with the Sensor implant taking an average of 7 minutes. From a femoral approach, the SG catheter tended to go the left pulmonary artery and the majority of sensors were implanted in a pulmonary artery branch in the left lung (94.2%) as shown in Table 16.

Table 16. Sensor Implant Information

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)	p-value
Total Procedure Time (mins)				
Mean±StdDev (N)	54.3±32.5 (270)	54.2±30.8 (280)	54.3±31.6 (550)	0.7424
(95% CI)	(50.4 - 58.2)	(50.6 - 57.9)	(51.6 - 56.9)	
Location of Sensor [2]				
Right Lung	14 (5.2%)	18 (6.4%)	32 (5.8%)	0.5875
Left Lung	256 (94.8%)	262 (93.6%)	518 (94.2%)	

[1] P-value testing Treatment vs. Control obtained from exact Wilcoxon Rank-Sum Test for continuous measures and Fisher's exact test for categorical measures.
[2] Comparison of right lung versus left lung.

Bland Altman Analysis at Implant

At the time of sensor implant, all patients underwent a standard right heart catheterization utilizing a Swan Ganz catheter. Due to the tendency for over and under damping of fluid filled catheters leading to inaccurate estimations of PA systolic and diastolic pressures, the PA mean pressure as measured by the Swan Ganz was used as the reference measurement. Following calibration to the mean PA pressure, additional pressure recordings were taken to confirm accuracy of the sensor.

Figure 10 summarizes the Bland-Altman analysis of the simultaneous PA mean pressure and reveals an average difference of 0.1 mmHg (95% limits of agreement of -2.0 and 2.2 mmHg). Regression analysis (Figure 11) showed good correlation (r=0.99).

Figure 10. Bland-Altman Plot – PA Mean Pressure

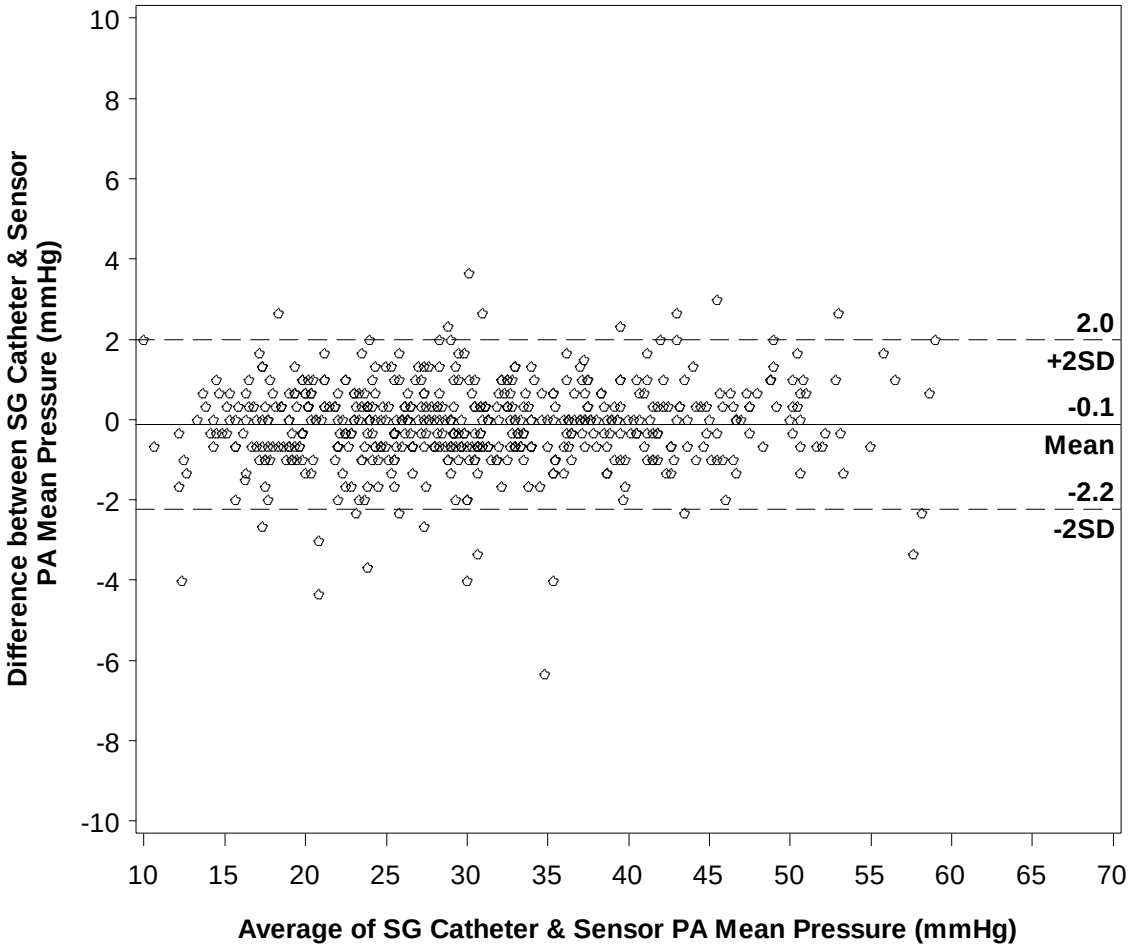
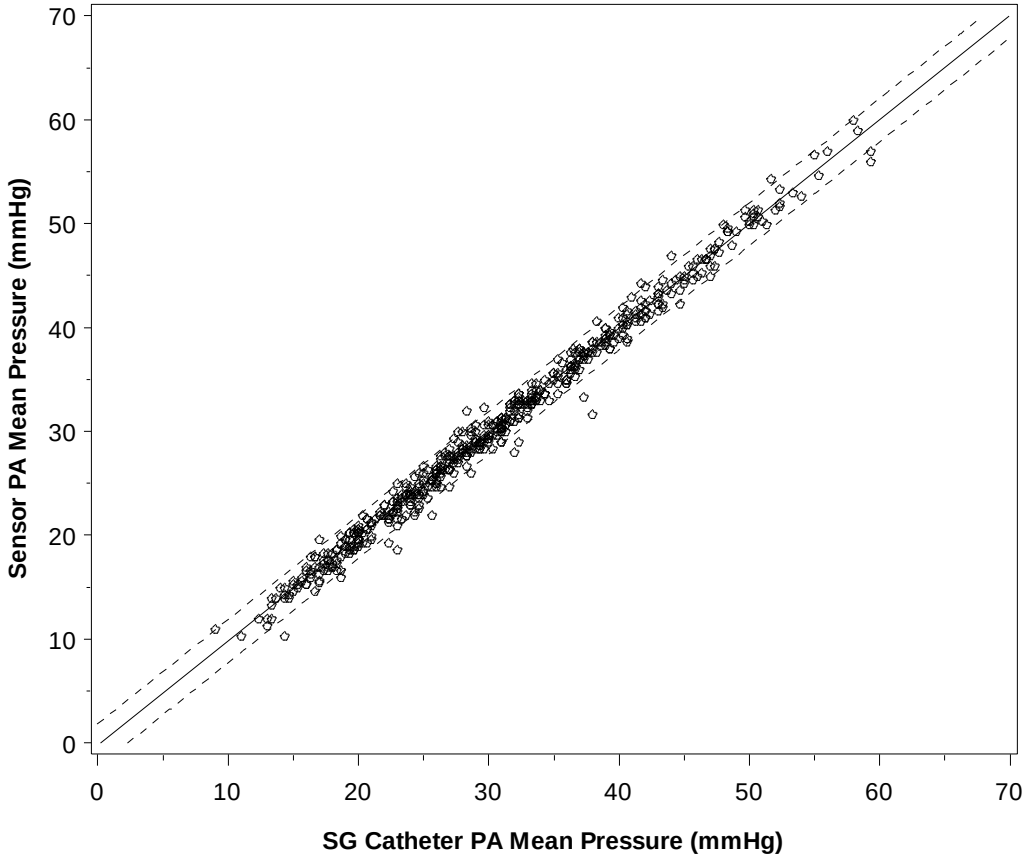


Figure 11. Linear Regression Plot – PA Mean Pressure



10.7 Primary and Secondary Analyses

10.7.1 Primary Safety

Table 17 summarizes the first primary safety endpoint of freedom from a device/system-related (DSRC) complication up to the 6 month follow-up visit. Of the 575 patients who were consented and had an attempted right heart catheterization, 567 (98.6%) were free from DSRC. The exact 95.2% lower and upper confidence limits were 97.3% and 99.4%, respectively. When compared to the pre-specified objective performance criterion of 80%, the freedom from DSRC was highly significant with p<0.0001, indicating that the implant procedure was safe.

Table 17. First Primary Safety Endpoint - Device/System Related Complications

	CONSENTED NOT RANDOMIZED N=25	TREATMENT N=270	CONTROL N=280	ALL PATIENTS N=575	p-value [2]
Device/System Related Complication [1]					
N (%) Exact 95.2% Confidence Interval [3]	2 (8.0%)	3 (1.1%)	3 (1.1%)	8 (1.4%) (0.6%-2.7%)	<0.0001
Freedom from Device/System Related Complication					
N (%) Exact 95.2% Confidence Interval [3]	N/A	N/A	N/A	567 (98.6%) (97.3%-99.4%)	N/A

[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.
[2] P-value from exact test of binomial proportions compared to 0.20 for All Patients
[3] Exact (Clopper-Pearson) confidence limits

Device/System-related Complications Details

Table 18 lists the 8 DSRCs as adjudicated by the CEC which comprise the first primary safety endpoint. A device /system-related complication was defined in the protocol as 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 subject
- results in the explant of the device

In 6 of the 8 events, the patient recovered from the complication without permanent disability or sequelae. Two patients, who retrospectively were very ill at the time of the implant, expired. One patient had complications of sepsis contributed to worsening respiratory distress

and hemodynamic instability and the other a complication of an atrial dysrhythmia leading to worsening hemodynamics. In both cases, despite aggressive initial therapy, the family requested a change in status to DNR and care was withdrawn. Neither death was adjudicated by the CEC as related to the device/system. One of the two events of failure of sensor release was adjudicated as a DSRC due to the need for additional intervention.

Table 18. Device / System Related Complications – CEC adjudication

Adjudication	Complication	Days after implant	Description and Therapy	Outcome
Definitely	Sensor did not fully deploy	During Implant	Sensor remained attached to delivery catheter. Therapy: sensor removed with snare during same procedure. Patient discharged next day	**Recovered without sequela**
Definitely	In-situ thrombus	14	CTA revealed a small thrombus in a non-sensor PA branch secondary to over-inflation of the Swan-Ganz balloon. Thrombus not associated with sensor. Therapy: adjusted anticoagulation	**Recovered without sequela**
Possibly	Hemoptysis	During Implant	Chronic cough exacerbated during implant. Bronchoscopy revealed well formed thrombus, in non-implant lung, positive for Klebsiella. Therapy: irrigation, suction, antibiotics	**Recovered without sequela**
Possibly	Atypical Chest Pain	1	ECG normal and isoenzymes negative. Therapy: nitrates and analgesics	**Recovered without sequela**
Possibly	TIA	8	History of Afib, INR subtherapeutic. Therapy: warfarin adjusted to obtain therapeutic INR	**Recovered without sequela**
Possibly	Arterial embolism	10	History of A-Fib, INR was subtherapuetic; Right arm arterial thrombus. Therapy: thrombectomy and adjusted anticoagulation	**Recovered without sequela**
Possibly	Sepsis	1	HIV, Hep C, worsening respiratory distress, hemodynamic instability, sepsis. Therapy: antibiotics, inotropes, nebulizers	**DNR; care withdrawn**
Possibly	Atrial Dysrhythmia	1	Arrhythmia lead to worsening cardiopulmonary status. Therapy: amiodarone, diuretics, dopamine	**DNR; care withdrawn**

The second primary safety endpoint of pressure sensor failures up to 6 months of follow-up is summarized in Table 19. Of the 550 sensors implanted, all (100%) were operational at 6 months and there were no sensor explants or repeat implants. When compared to the pre-specified objective performance criterion of 90%, these rates were highly significant with p<0.0001 level, indicating that this trial met the second primary safety endpoint with no pressure sensor failures.

Table 19. Second Primary Safety Endpoint - Pressure Sensor Failures

	TREATMENT N=270	CONTROL N=280	ALL PATIENTS N=550	p-value[2]
Pressure Sensor Failure [1]				
N (%) Exact 95.2% Confidence Interval [3]	0 (0.0%)	0 (0.0%)	0 (0.0%) (0%-0.7%)	<0.0001
Freedom from Pressure Sensor Failure				
N (%) Exact 95.2% Confidence Interval [3]	N/A	N/A	550 (100%) (99.3%-100.0%)	N/A

[1] A pressure sensor failure occurs when readings cannot be obtained after troubleshooting of the system
[2] P-value from exact test of binomial proportions compared to 0.10 for All Patients
[3] Exact (Clopper-Pearson) confidence limits

10.7.2 Analysis of Primary Safety After 6 Months

After the 6 month visit, all 498 (100%) patients were free of DSRCs. When compared to the objective performance criterion of 80%, the freedom from DSRCs was highly significant with p<0.0001 as shown in Table 20. All DSRCs occurred in the immediate peri-implant time period indicating that there is minimal risk of a DSRC after 6 months.

Table 20. Device/System Related Complications after 6 Month Follow-Up Visit

	CONSENTED NOT RANDOMIZED N=0	TREATMENT N=244	CONTROL N=254	ALL PATIENTS N=498	p-value [2]
Device/System Related Complication [1]					
N (%) Exact 95.2% Confidence Interval [3]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%) (0%-0.7%)	<0.0001
Freedom from Device/System Related Complication					
N (%) Exact 95.2% Confidence Interval [3]	N/A	N/A	N/A	498 (99.3%-100.0%)	N/A

[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.
[2] P-value from exact test of binomial proportions compared to 0.20 for All Patients
[3] Exact (Clopper-Pearson) confidence limits

Of the 550 patients with sensors implanted, all (100%) had operational sensors after 6 months and through study duration as shown in Table 21. When compared to the established objective performance criterion of 90%, these rates were highly significant with p<0.0001.

Table 21. Pressure Sensor Failures After 6 Months Follow-Up Visit

	TREATMENT N=244	CONTROL N=254	ALL PATIENTS N=498	p-value[2]
Pressure Sensor Failure [1]				
N (%) Exact 95.2% Confidence Interval [3]	0 (0.0%)	0 (0.0%)	0 (0.0%) (0%-0.7%)	<0.0001
Freedom from Pressure Sensor Failure				
N (%) Exact 95.2% Confidence Interval [3]	N/A	N/A	498 (100%) (99.3%-100.0%)	N/A

[1] A pressure sensor failure occurs when readings cannot be obtained after troubleshooting of the system
[2] P-value from exact test of binomial proportions compared to 0.10 for All Patients
[3] Exact (Clopper-Pearson) confidence limits

10.7.3 Primary Efficacy

The primary efficacy endpoint of the rate of HF hospitalizations up to 6 months of follow-up is presented within Table 22. In the control group, there were a total of 120 heart failure hospitalizations in 280 patients, indicating an overall hospitalization rate of 0.44 hospitalizations/patient-6 months. In the treatment group, there were 84 hospitalizations among 270 patients, indicating an overall rate of 0.32 hospitalizations/patient-6 months. Thus, the treatment group had a highly significant (p=0.0002) 28% relative risk reduction in HF hospitalizations and the trial met its primary endpoint.

In addition, the NNT (number needed to treat) to prevent one HF hospitalization was 8 which compares favorably with published results in clinical trials of neurohormonal and CRT device heart failure trials (Jessup, 2009).

Table 22. Primary Efficacy Endpoint Rate of Heart Failure Hospitalizations

	TREATMENT (270)		CONTROL (280)		ALL PATIENTS (550)		
	# Hosp.	**Hosp. Rate** (events/ patient-6 mo.)	**# Hosp.**	**Hosp. Rate** (events/ patient-6 mo.)	**NBR p-value[1]**	**RRR**	**NNT**
Up to 6 Months	84	0.32	120	0.44	0.0002	28%	8

[1] P-value from the test for $\beta_1 = 0$ in the negative binomial regression (NBR) model.
NNT = Number needed to treat, RRR = Relative Risk Reduction

10.7.4 Analysis of Primary Efficacy over Study Duration

The cumulative HF hospitalizations over the study duration (entire blinded randomized follow-up) are presented in Table 23 and Figure 12. At 6 months (primary endpoint duration), there is a clear separation between the groups, and they continue to diverge over the entire duration of follow-up. Based on the negative binomial regression analysis, the difference between the treatment and control groups was highly significant with p<0.0001. The treatment effect was durable with the treatment group having a continued relative decrease (37%) in HF hospitalizations and the NNT was very low at 4. The treatment effect was particularly dramatic after 6 months with a 45% RRR in favor of the treatment group.

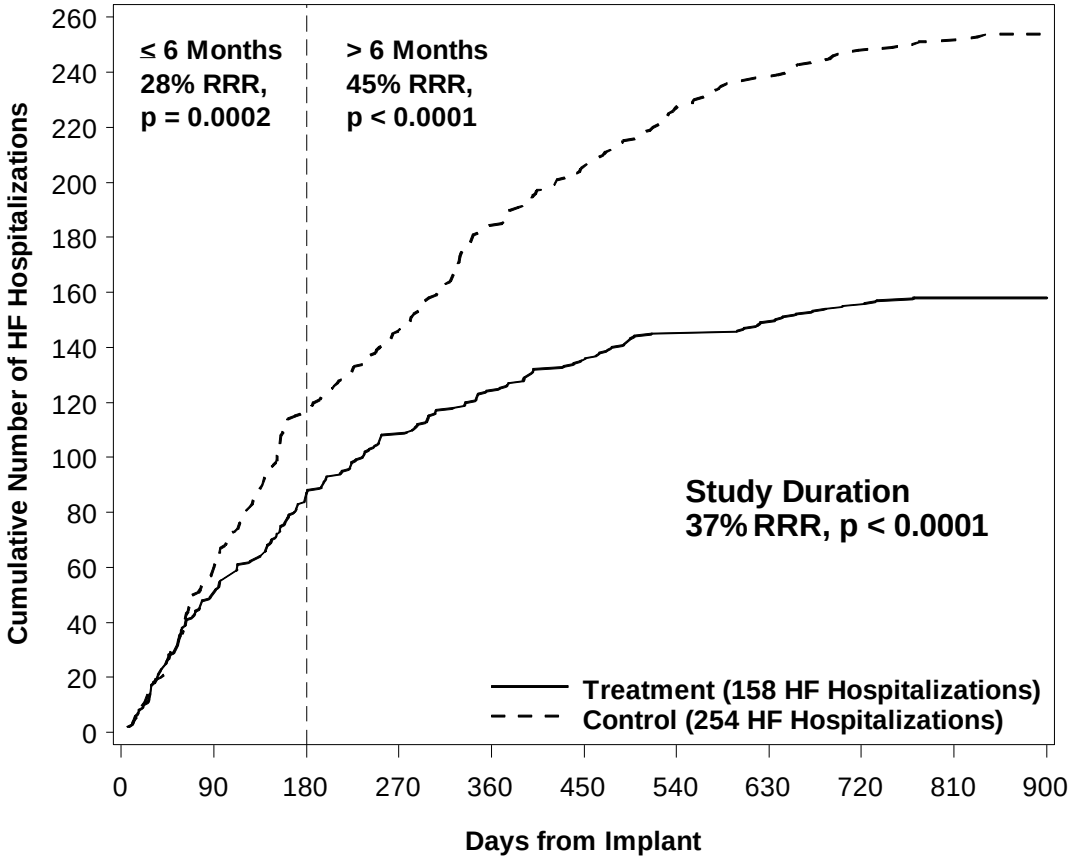
An additional pre-specified supplementary analysis within the statistical analysis plan (SAP) was performed using the Andersen-Gill extension of the Cox Regression model). The hazard ratio of treatment to control was 0.63 (95% CI 0.52 – 0.77; p<0.0001) showing a significant reduction in the distribution of hospitalizations over the study duration.

Table 23. Supplementary Analyses of Rate of HF Hospitalizations over the Study Duration

	TREATMENT (270)		CONTROL (280)		ALL PATIENTS (550)			
	# Hosp.	**Hosp. Rate** (events/ patient-year)	**# Hosp.**	**Hosp. Rate** (events/ patient-year)	**NBR p-value[1]**	**RRR**	**NNT**	**A-G p-value[2] / Hazard Ratio (95% CI)**
After 6 Months	74	0.35 (0.17 6m rate)	134	0.63 (0.31 6m rate)	<0.0001	45%	4	<0.0001 / 0.55 (0.42-0.73)
Study Duration	158	0.46	254	0.73	<0.0001	37%	4	<0.0001 / 0.63 (0.52-0.77)

[1] P-value from the negative binomial regression (NBR) model.
[2] p-value / Hazard ratio (Treatment to Control) and 95% Confidence Interval from the Andersen-Gill (A-G) model.
Duration of Follow-up Mean 454.8 days (15.2 months) ± 211.3 days Range (1-931 Days)
NNT = Number needed to treat, RRR = Relative Risk Reduction
After 6 months: N=244 (treatment group), N=254 (control group)

Figure 12. Cumulative Heart Failure Hospitalizations Over the Study Duration



No. at Risk											
Treatment	270	262	244	210	169	131	108	82	29	5	1
Control	280	267	252	215	179	137	105	67	25	10	0

10.7.5 Secondary Efficacy

Secondary efficacy endpoints were analyzed at the 6 month visit. The secondary efficacy variables and their hierarchical order of testing were as follows:

1. Change from baseline in pulmonary artery mean pressures
2. Proportion of subjects hospitalized for heart failure
3. Days alive outside of the hospital (for HF hospitalization)
4. Quality of Life - Minnesota Living with Heart Failure Questionnaire (MLHFQ)

Change from Baseline in Pulmonary Artery 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 pressure (first seven days of home readings)

served as the reference point; a positive AUC indicates PA mean pressures higher than the baseline and a negative AUC indicates PA mean pressures lower than the baseline.

The treatment and control patients had similar baseline PA pressures. Over 6 months of follow-up, however, the treatment group had a reduction in pressures with an AUC of -155.7 mmHg days, compared to the control group which had an increase in pressures with an AUC of 33.1 mmHg days (Table 24). This difference was significant with p=0.0077.

Patients at high risk for decompensation and hospitalization are hemodynamically characterized by high filling pressures and persistent increases in pressures over time. This provides the basis for the hypothesis that hemodynamically guided heart failure management is superior to traditional clinical tools, such as physical examination or daily weights. This hypothesis suggests that patients' hospitalization risks are increased in relation to the duration of the elevated pressures. Since daily pressures have normal variability (Adamson, et al., 2003), point-in-time values are inadequate to draw conclusions about the effect of therapy over time. Therefore, the change in pressure is expressed as the area under the pressure curve over 6 months relative to baseline. Unlike other summary measures such as baseline value, average, or maximum, both the magnitude of the response and its changes over time are captured through the use of AUC.

Thus, these data suggest that reduction in PA mean pressure leads to reduction in HF hospitalizations. The control group experienced a slight increase in PA mean pressure AUC during the follow-up period. In contrast, the treatment group experienced significant decreases in PA mean pressure AUC with a corresponding 28% relative risk reduction in the rate of HF hospitalizations.

Table 24. Secondary Efficacy Endpoint - Change from Baseline in Pulmonary Artery Mean Pressures at 6 Months

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)	p-value
Change from Baseline (AUC) [4]				
Mean±StdDev (N)	-155.7±1,088.0 (265)	33.1±951.7 (272)	-60.1±1,024.6 (537)	0.0077
(95% CI)	(-287.3 - -24.1)	(-80.5 - 146.7)	(-146.9 - 26.8)	

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

Proportion of Subjects Hospitalized for Heart Failure

The proportion of patients hospitalized with a HF hospitalization is presented in Table 25. During the 6 month follow up period, 55 (20.4%) out of 270 and 80 (28.6%) out of 280 control patients suffered a HF hospitalization (p=0.0292). Thus, this secondary endpoint was met.

Consistency in treatment effect was found between analyses of proportion of patients with at least one HF hospitalization and rates of hospitalization indicating a robust treatment effect. The treatment group not only had fewer HF hospitalizations (primary endpoint) but also had fewer patients hospitalized for HF (secondary endpoint).

Table 25. Secondary Efficacy Endpoint - Proportion of Subjects Hospitalized for Heart Failure at 6 Months

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

Days Alive Outside of the Hospital (HF Hospitalizations)

Days alive outside of the hospital defined as days without a HF hospitalization is summarized in Table 26. 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, which was significant(p=0.0280). Further, 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 (p=0.0246).

Thus, efficacy was consistent in the rate of hospitalizations, number of patients hospitalized, and the number of days alive outside of the hospital.

Table 26. Secondary Efficacy Endpoint – Days Alive Outside of the Hospital up to 6 Month Visit

	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]
(95% CI)	(173.1 - 180.2)	(171.8 - 180.1)	(173.5 - 179.0)	
Total	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]
(95% CI)	(170.7 - 178.2)	(167.7 - 176.6)	(170.4 - 176.2)	
Total	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]
(95% CI)	(1.4 - 3.0)	(2.5 - 5.1)	(2.2 - 3.8)	
Total	589	1,058	1,647	

[1] P-value from Wilcoxon Rank Sum test
[2] P-value from Wilcoxon Rank Sum test after controlling for subject duration in study
(i.e., Days Alive Outside Hospital / Subject Durationx180)
A few patients had 6 month visit deviations which account for the large number of follow-up days

Quality of Life- MLHFQ

Secondary Efficacy Endpoint – Quality of Life: MLHFQ Total Score

Heart failure specific quality of life was assessed with the MLHFQ total score at 6 months (Table 27). The average total score in the treatment group was 45.2 ± 26.4 which was significantly better than the average total score in the control group 50.6 ± 24.8 (p=0.0236). The difference in total quality of life was primarily due to the physical domain (Table 28). The average physical score for the treatment group (19.8 ± 11.2) was significantly better than the control group (22.4 ± 10.9) (p=0.0096). There was also a significant difference in the emotional domain with an average score of 9.5 ± 8.1 for the treatment group and 11.0 ± 7.7 for the control group (p=0.0398) (Table 29).

Table 27. Secondary Efficacy Endpoint – Quality of Life: MLHFQ Total Score 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
(95% CI)	(41.8 - 48.7)	(47.4 - 53.8)	(45.6 - 50.3)	

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

Table 28. Quality of Life – MLHFQ Physical Score at 6 Months

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)	p-value[1]
6 Month Follow-up - Physical Score				
Mean±StdDev (N)	19.8±11.2 (229)	22.4±10.9 (236)	21.1±11.1 (465)	0.0096
(95% CI)	(18.3 - 21.2)	(21.0 - 23.8)	(20.1 - 22.1)	

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

Table 29. Quality of Life – MLHFQ Emotional Score at 6 Months

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)	p-value[1]
6 Month Follow-up - Emotional Score				
Mean±StdDev (N)	9.5±8.1 (229)	11.0±7.7 (236)	10.2±7.9 (465)	0.0398
(95% CI)	(8.4 - 10.5)	(10.0 - 12.0)	(9.5 - 11.0)	

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

10.7.6 Supplementary Analysis of Secondary Efficacy Over Study Duration

Supplementary analyses of secondary efficacy endpoints over the study duration were as follows:

1. Change from baseline in pulmonary artery mean pressures
2. Proportion of subjects hospitalized for heart failure
3. Days alive outside of the hospital (for HF hospitalization)
4. Quality of Life Minnesota Living with Heart Failure Questionnaire (MLHFQ)

Change from baseline in pulmonary artery mean pressures at 12 Months

To control for variable lengths of follow-up information after 6 months and to achieve unbiased estimates of the PA pressure AUC, analysis was fixed at 12 months of follow-up. The same PA pressure analysis was completed over 12 months of follow-up and a pattern similar to the 6 month analysis was observed (Table 30). Table 30 shows that the treatment group had an average reduction in AUC of 201.5 mmHg days compared to an increase of 106.5 mmHg days in the control group (p=0.0299). Thus, the reduction in PA mean pressure was maintained at 12 months of follow-up.

Table 30. Supplementary Analysis - Change from Baseline in Pulmonary Artery Mean Pressures at 12 Months

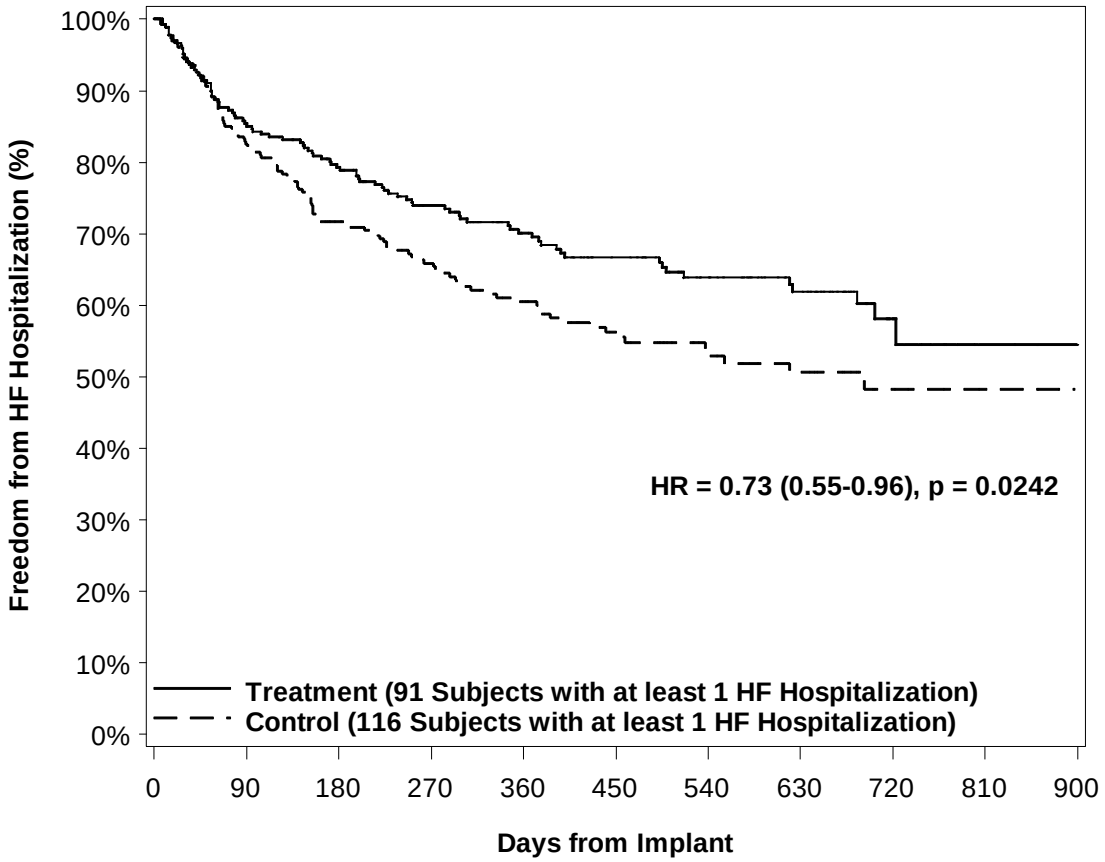
	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)	p-value
Change from Baseline (AUC) [1]				
Mean±StdDev (N)	-201.5±2082.8 (265)	106.5±2127 (272)	-46.8±2120 (537)	0.0299
(95% CI)	(-453.4 - 50.4)	(-147.3 - 360.4)	(-224.2 - 133.3)	

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

Proportion of Subjects Hospitalized for Heart Failure over Study Duration

The treatment group experienced a greater proportion of patients having freedom from hospitalization than the control group, over the entire follow-up period (p = 0.0242) (Figure 13).

Figure 13. Freedom from HF Hospitalization Over the Study Duration



No. at Risk											
Treatment	270	225	201	168	130	104	83	62	17	4	1
Control	280	223	186	145	112	79	56	38	13	6	0

Days Alive Outside of the Hospital over Study Duration

Days alive outside of the hospital (days without HF hospitalizations) is summarized in Table 31. Treatment patients spent fewer days in the hospital (4.3 ± 10.9) than control patients (6.7 ± 13.8) (p=0.0190). In addition, over the study duration the treatment group spent 726 fewer days in the hospital than the control patients (1,881 days control – 1,155 days treatment).

For the treatment group, the average number of days alive outside the hospital was 455.4 ± 212.8 days compared to 443.3 ±211.0 days for the control group (p=0.0425); thus the treatment group had 12 more days alive outside of the hospital. The benefit to the treatment group for days alive outside of the hospital increased over the course of the study from 2.3 days at 6 months to 12 days at 15 months mean follow up.

Table 31. Supplementary Analysis – Days Alive Outside of the Hospital Over the Study Duration

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)	p-value
Total Days Alive				
Mean±StdDev (N)	459.7±212.4 (270)	450.0±210.6 (280)	454.8±211.3 (550)	0.5784 [1]
(95% CI)	(434.2 - 485.1)	(425.3 - 474.8)	(437.1 - 472.5)	
Total	124,108	126,007	250,115	
Days Alive Outside Hospital				
Mean±StdDev (N)	455.4±212.8 (270)	443.3±211.0 (280)	449.2±211.8 (550)	0.0425 [2]
(95% CI)	(429.9 - 480.9)	(418.5 - 468.1)	(431.5 - 467.0)	
Total	122,953	124,126	247,079	
Days Hospitalized				
Mean±StdDev (N)	4.3±10.9 (270)	6.7±13.8 (280)	5.5±12.5 (550)	0.0190 [1]
(95% CI)	(3.0 - 5.6)	(5.1 - 8.3)	(4.5 - 6.6)	
Total	1,155	1,881	3,036	

[1] P-value from Wilcoxon Rank Sum test
[2] P-value from Wilcoxon Rank Sum test after controlling for subject duration in study
(i.e., Days Alive Outside Hospital / Subject Durationx455)

Quality of Life - MLHFQ at 12 Months

The MLHFQ total, physical, and emotional scores at 12 months in the treatment group were lower than in the control group, but not statistically significant (Table 32).

Table 32. Quality of Life (MLHFQ) at 12 Months

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)	p-value[1]
Total Score				
Mean±StdDev (N)	46.4±26.0 (155)	50.1±25.1 (169)	48.3±25.5 (324)	0.1992
(95% CI)	(42.3 - 50.5)	(46.3 - 53.9)	(45.5 - 51.1)	
Physical Score				
Mean±StdDev (N)	20.2±10.8 (155)	21.7±10.9 (169)	21.0±10.8 (324)	0.2061
(95% CI)	(18.5 - 21.9)	(20.1 - 23.4)	(19.8 - 22.2)	
Emotional Score				
Mean±StdDev (N)	10.2±7.8 (155)	10.7±7.8 (169)	10.5±7.8 (324)	0.5107
(95% CI)	(8.9 - 11.4)	(9.5 - 11.9)	(9.6 - 11.3)	
Total Score Change from Baseline				
Mean±StdDev (N)	-7.7±24.1 (155)	-7.3±27.5 (169)	-7.5±25.9 (324)	0.4126
(95% CI)	(-11.5 - -3.8)	(-11.5 - -3.1)	(-10.3 - -4.7)	
Physical Score Change from Baseline				
Mean±StdDev (N)	-3.3±10.2 (155)	-3.0±11.8 (169)	-3.1±11.1 (324)	0.3923
(95% CI)	(-4.9 - -1.6)	(-4.8 - -1.2)	(-4.3 - -1.9)	
Emotional Score Change from Baseline				
Mean±StdDev (N)	-1.3±7.2 (155)	-1.6±7.9 (169)	-1.4±7.6 (324)	0.9114
(95% CI)	(-2.4 - -0.1)	(-2.8 - -0.4)	(-2.3 - -0.6)	

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

Lack of significance at the 12 month analysis is most likely due to reduced power secondary to the large number of patients (226) who had not completed the 12 month follow-up visit at the time of database lock. Therefore a conservative data imputation analysis (LOCF) was performed and demonstrates better quality of life in the treatment group at 12 months (Table 33).

Table 33. Quality of Life (MLHFQ) at 12 Months – LOCF imputed

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)	p-value[1]
Total Score				
Mean±StdDev (N)	47.7±27.3 (270)	52.7±25.0 (280)	50.2±26.3 (550)	0.0267
(95% CI)	(44.4 - 51.0)	(49.7 - 55.6)	(48.0 - 52.4)	
Physical Score				
Mean±StdDev (N)	20.6±11.5 (270)	23.0±11.0 (280)	21.8±11.3 (550)	0.0154
(95% CI)	(19.2 - 22.0)	(21.7 - 24.2)	(20.9 - 22.8)	
Emotional Score				
Mean±StdDev (N)	10.5±8.2 (270)	11.5±7.6 (280)	11.0±7.9 (550)	0.1500
(95% CI)	(9.5 - 11.5)	(10.6 - 12.4)	(10.3 - 11.7)	
Total Score Change from Baseline				
Mean±StdDev (N)	-8.9±25.3 (270)	-6.8±25.5 (280)	-7.8±25.4 (550)	0.0732
(95% CI)	(-11.9 - -5.9)	(-9.8 - -3.8)	(-9.9 - -5.7)	
Physical Score Change from Baseline				
Mean±StdDev (N)	-3.9±11.0 (270)	-2.6±11.3 (280)	-3.2±11.2 (550)	0.0298
(95% CI)	(-5.2 - -2.6)	(-3.9 - -1.2)	(-4.2 - -2.3)	
Emotional Score Change from Baseline				
Mean±StdDev (N)	-1.5±7.4 (270)	-1.4±7.4 (280)	-1.5±7.4 (550)	0.4012
(95% CI)	(-2.4 - -0.6)	(-2.3 - -0.6)	(-2.1 - -0.8)	

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

10.8 Pre-specified Subgroup Analysis

10.8.1 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%. Table 34 and Table 35 summarize the demographics in the two groups. Overall, there were no significant differences in baseline characteristics between the treatment and control patients in either of these 2 subgroups.

Table 34. Screening Demographics and Assessments – Reduced Ejection Fraction (EF<40%)

	TREATMENT (208)	CONTROL (222)	ALL PATIENTS (430)	p-value
Age (years)				
Mean±StdDev (N)	59.7±13.0 (208)	61.0±12.7 (222)	60.4±12.8 (430)	0.2424
(95% CI)	(57.9 - 61.5)	(59.3 - 62.7)	(59.2 - 61.6)	
Gender				
Male	157 (75.5%)	170 (76.6%)	327 (76.0%)	0.8216
Female	51 (24.5%)	52 (23.4%)	103 (24.0%)	
Race				
White	142 (68.3%)	161 (72.5%)	303 (70.5%)	0.3431[2]
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%)	1.0000
Non-Hispanic	197 (94.7%)	211 (95.0%)	408 (94.9%)	
BMI				
Mean±StdDev (N)	30.2±6.0 (208)	30.1±6.4 (222)	30.1±6.2 (430)	0.9944
(95% CI)	(29.4 - 31.0)	(29.3 - 31.0)	(29.6 - 30.7)	
BMI > 35				
Yes	44 (21.2%)	45 (20.3%)	89 (20.7%)	0.9053
No	164 (78.8%)	177 (79.7%)	341 (79.3%)	
Chest Circumference				
< 52	25 (12.0%)	34 (15.3%)	59 (13.7%)	0.0751
>=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%)	N/A
Class II	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Class III	208 (100.0%)	222 (100.0%)	430 (100.0%)	
Class IV	0 (0.0%)	0 (0.0%)	0 (0.0%)	
CRT or CRT-D				

	TREATMENT (208)	CONTROL (222)	ALL PATIENTS (430)	p-value
Yes	82 (39.4%)	89 (40.1%)	171 (39.8%)	0.9216
No	126 (60.6%)	133 (59.9%)	259 (60.2%)	
ICD				
Yes	79 (38.0%)	87 (39.2%)	166 (38.6%)	0.8430
No	129 (62.0%)	135 (60.8%)	264 (61.4%)	
Ischemic Cardiomyopathy				
Yes	127 (61.1%)	143 (64.4%)	270 (62.8%)	0.4861
No	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)	0.4169
(95% CI)	(1.36 - 1.49)	(1.31 - 1.42)	(1.35 - 1.44)	
GFR (mL/min/1.73m²)				
Mean±StdDev (N)	61.1±23.4 (208)	62.6±23.6 (222)	61.9±23.5 (430)	0.5556
(95% CI)	(58.0 - 64.3)	(59.5 - 65.7)	(59.7 - 64.1)	

[1] P-value testing Treatment vs. Control
[2] Comparison of White versus non-white

Table 35. Screening Demographics and Assessments – Preserved Ejection Fraction (EF≥40%)

	TREATMENT (62)	CONTROL (57)	ALL PATIENTS (119)	p-value
Age (years)				
Mean±StdDev (N)	66.8±11.4 (62)	65.4±12.1 (57)	66.1±11.7 (119)	0.4804
(95% CI)	(63.9 - 69.7)	(62.2 - 68.6)	(64.0 - 68.2)	
Gender				
Male	37 (59.7%)	34 (59.6%)	71 (59.7%)	1.0000
Female	25 (40.3%)	23 (40.4%)	48 (40.3%)	
Race				
White	54 (87.1%)	43 (75.4%)	97 (81.5%)	0.1552[2]
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%)	0.1151
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)	0.4143
(95% CI)	(30.9 - 34.8)	(32.0 - 37.0)	(32.1 - 35.2)	
BMI > 35				
Yes	20 (32.3%)	20 (35.1%)	40 (33.6%)	0.8464
No	42 (67.7%)	37 (64.9%)	79 (66.4%)	
Chest Circumference				
< 52	17 (27.4%)	14 (24.6%)	31 (26.1%)	0.4506
>=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%)	N/A
Class II	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Class III	62 (100.0%)	57 (100.0%)	119 (100.0%)	
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%)	1.0000
No	53 (85.5%)	48 (84.2%)	101 (84.9%)	
ICD				
Yes	9 (14.5%)	11 (19.3%)	20 (16.8%)	0.6246
No	53 (85.5%)	46 (80.7%)	99 (83.2%)	
Ischemic Cardiomyopathy				
Yes	31 (50.0%)	31 (54.4%)	62 (52.1%)	0.7143
No	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)	0.6356
(95% CI)	(1.22 - 1.39)	(1.24 - 1.44)	(1.26 - 1.38)	
GFR (mL/min/1.73m²)				

	TREATMENT (62)	CONTROL (57)	ALL PATIENTS (119)	p-value
Mean±StdDev (N)	57.9±19.3 (62)	57.7±21.1 (57)	57.8±20.1 (119)	0.6808
(95% CI)	(53.0 - 62.8)	(52.1 - 63.3)	(54.2 - 61.5)	

[1] P-value testing Treatment vs. Control
[2] Comparison of White versus non-white

Patients with preserved ejection fraction had a mean EF of 51% and patients with reduced ejection fraction had a mean EF of 23%. There were no statistically significant differences in baseline ACE/ARB and beta blocker use between treatment and control patients in either the preserved or reduced ejection fraction groups. 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 36).

Table 36. Baseline Neurohormonal Medications by Baseline Ejection Fraction

	TREATMENT	CONTROL	ALL PATIENTS	p-value
Baseline in Full Subject Population	(270)	(280)	(550)	
ACE/ARB	205 (75.9%)	222 (79.3%)	427 (77.6%)	0.3584
Beta Blocker	243 (90.0%)	256 (91.4%)	499 (90.5%)	0.6595
Baseline in Reduced Ejection Fraction Population (EF<40%)	(208)	(222)	(430)	
ACE/ARB	163 (78.4%)	176 (79.3%)	339 (78.8%)	0.9060
Beta Blocker	193 (92.8%)	208 (93.7%)	401 (93.3%)	0.8478
Baseline in Preserved Ejection Fraction Population (EF ≥ 40%)	(62)	(57)	(119)	
ACE/ARB	42 (67.7%)	45 (78.9%)	87 (73.1%)	0.2153
Beta Blocker	50 (80.6%)	47 (82.5%)	97 (81.5%)	0.8181

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 (Table 37 and Figure 14). In contrast, the control group had 101 hospitalizations among 223 patients, yielding a rate of 0.47, hospitalization/patient-6 months, which was significantly higher than the treatment group (p=0.0074).

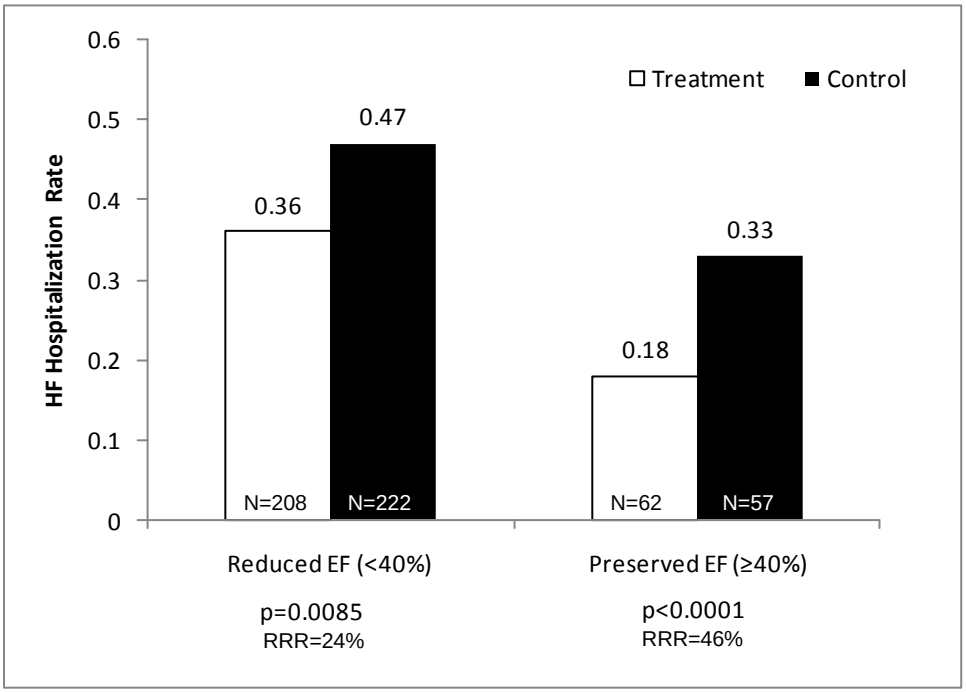
In the patients with preserved ejection fraction, the overall rate of hospitalization tended to be lower than that observed with patients with reduced ejection fraction. Nonetheless, the treatment benefit was still significant. The treatment group had 11 hospitalizations among 62 patients, yielding a 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 significantly higher than the treatment group (p<0.0001). These results demonstrate that HF management

based on PAP is effective in reducing HF hospitalizations in patients with either reduced or preserved LV function and this trial represents one of the first successful management strategies to reduce hospitalization risks for heart failure patients with preserved ejection fraction.

Table 37. Analysis of Rate of HF Hospitalizations at 6 Months by Baseline Ejection Fraction

	TREATMENT (270)			CONTROL (280)			ALL PATIENTS (550)	
	# Pts.	**# Hosp.**	**Hosp. Rate** (events/ patient-6 months)	**# Pts.**	**# Hosp.**	**Hosp. Rate** (events/ patient-6 months)	**NBR p-value[1]**	**RRR**
EF < 40%	208	73	0.36	222	101	0.47	0.0085	24%
EF ≥ 40%	62	11	0.18	57	19	0.33	<0.0001	46%
[1] P-value from the negative binomial regression (NBR) model.								

Figure 14. Hospitalizations by Baseline Preserved and Reduced Ejection Fraction

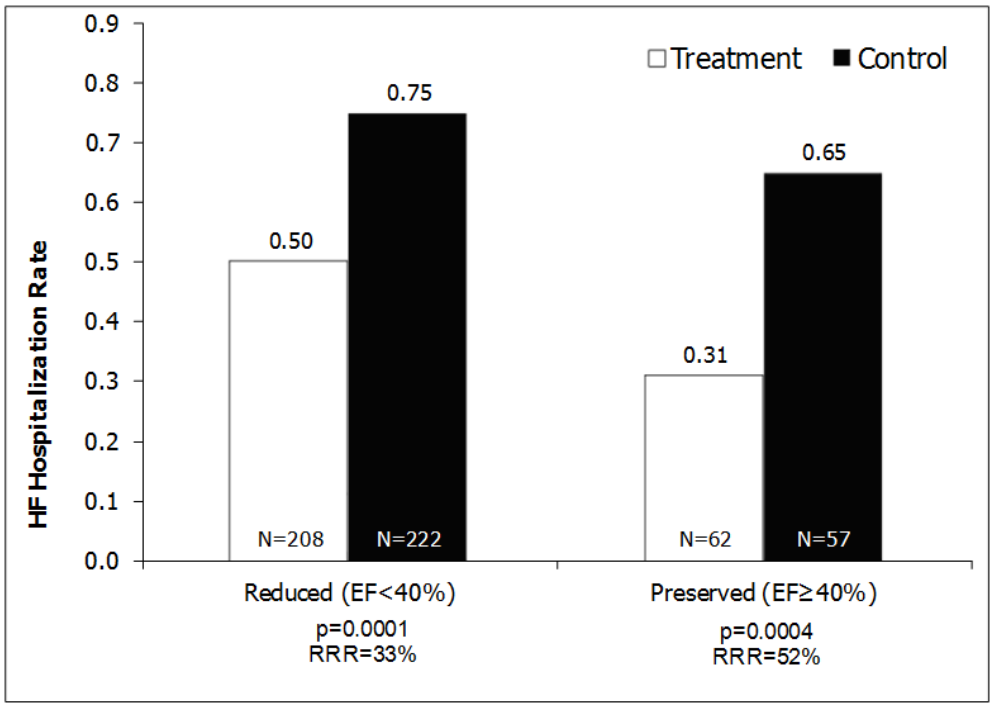


A supplementary analysis was performed by baseline ejection fraction over the study duration (Table 38 and Figure 15). As observed in the 6 months results, the treatment group had a lower rate of HF hospitalizations than the control group in both reduced EF (p=0.0001) and preserved EF (p=0.0004).

Table 38 Supplementary Analysis by Baseline Ejection Fraction – Study Duration

	TREATMENT (270)			CONTROL (280)			ALL PATIENTS (550)	
	# Pts.	**# Hosp.**	**Hosp. Rate** (events/ patient-year)	**# Pts.**	**# Hosp.**	**Hosp. Rate** (events/ patient-year)	**NBR p-value[1]**	**RRR**
EF < 40%	208	133	0.50	222	202	0.75	0.0001	33%
EF ≥ 40%	62	25	0.31	57	52	0.65	0.0004	52%
[1] P-value from the negative binomial regression (NBR) model.								

Figure 15. Hospitalizations by Baseline Preserved and Reduced Ejection Fraction – Study Duration



10.9 Additional Supplementary Analyses

10.9.1 Quality of Life: MLHFQ Change from Baseline

The MLHFQ is commonly analyzed by comparing the change from baseline. While this methodology is different from that used in the secondary efficacy endpoint, the total MLHFQ score change from baseline to the 6 month visit is provided below (Table 39). The treatment group had a greater improvement from baseline to 6 months than the control group (-10.6 vs. -7.4, respectively, p = 0.0373). Likewise, the change in physical score (Table 40) also shows greater improvement in the treatment group (-4.6) than in the control group (-2.5) (p = 0.0086). The change in emotional score for treatment (-2.2) was not significantly better than control (-1.6) (p = 0.0985) (Table 41).

Table 39. Supplementary Analysis – Quality of Life: MLHFQ Total Score Change from Baseline at 6 Months

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)	p-value[1]
6 Month Follow-up Change from Baseline				
Mean±StdDev (N)	-10.6±24.9 (229)	-7.4±24.9 (236)	-8.9±25.0 (465)	0.0373
(95% CI)	(-13.8 - -7.3)	(-10.6 - -4.2)	(-11.2 - -6.7)	

[1] P-value from analysis of covariance, with the Baseline value as a covariate

Table 40. Supplementary Analysis – Quality of Life: MLHFQ Physical Score Change from Baseline at 6 Months

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)	p-value[1]
6 Month Follow-up Change from Baseline				
Mean±StdDev (N)	-4.6±11.3 (229)	-2.5±11.4 (236)	-3.6±11.4 (465)	0.0086
(95% CI)	(-6.1 - -3.1)	(-4.0 - -1.1)	(-4.6 - -2.5)	

[1] P-value from analysis of covariance, with the Baseline value as a covariate

Table 41. Supplementary Analysis – Quality of Life: MLHFQ Emotional Score Change from Baseline at 6 Months

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)	p-value[1]
6 Month Follow-up Change from Baseline				
Mean±StdDev (N)	-2.2±7.3 (229)	-1.6±7.9 (236)	-1.9±7.6 (465)	0.0985
(95% CI)	(-3.1 - -1.2)	(-2.6 - -0.6)	(-2.6 - -1.2)	

[1] P-value from analysis of covariance, with the Baseline value as a covariate

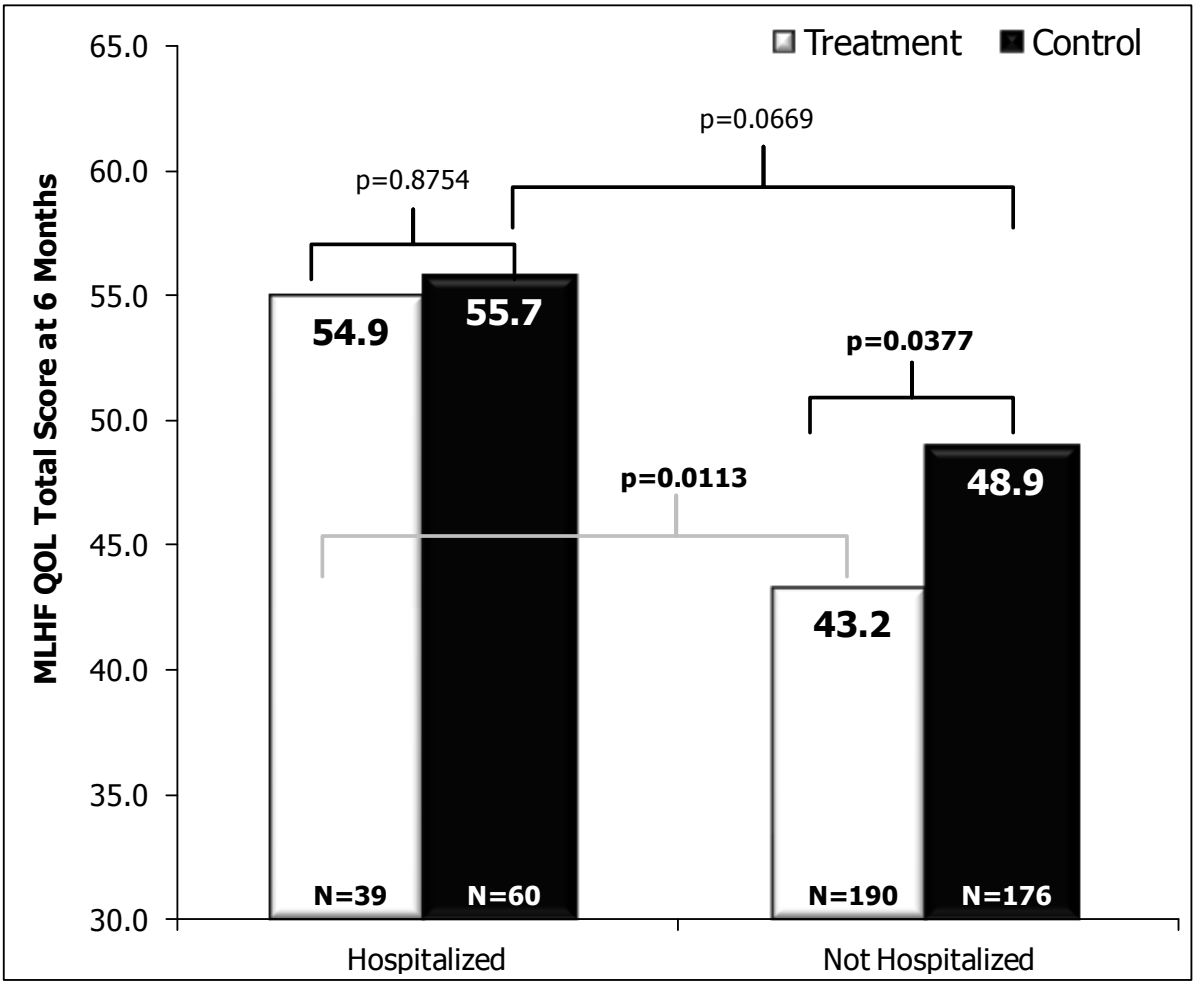
10.9.2 MLHFQ in Patients Hospitalized vs. Not Hospitalized

There was significantly higher quality of life in the treatment patients that were not hospitalized vs. those that had one or more HF hospitalizations (p=0.0113) (Figure 16). This difference was not significant in the control group (p=0.0669).

For patients that were not hospitalized, the treatment group experienced a significantly better QOL than the control group (p=0.0377).

For patients that were hospitalized, there were significantly fewer patients in the treatment group (39) than in control (60), (p=0.0313, Fisher's Exact test).

Figure 16. MLHFQ in Patients Hospitalized vs. Not Hospitalized



10.9.3 All Cause Hospitalizations up to 6 months

The objective of the CHAMPION study was to evaluate the safety and efficacy of the HF monitoring system in reducing HF hospitalizations. An independent, blinded clinical events committee (CEC) reviewed all adverse events and hospitalizations that occurred during the study. The CEC determined the predominant reason for hospitalization.

It was important to determine whether the reduction in HF hospitalizations was offset by an increase in non-HF hospitalizations. The analysis in Table 42 below summarizes all the hospitalizations that occurred over 6 months, separated into heart failure and non-heart failure hospitalizations.

During the 6 months primary efficacy period, the treatment group had 84 HF hospitalizations compared to 120 in the control group. During this same period the treatment group had 148 non-HF hospitalizations vs. the 143 non-HF hospitalizations in the control group (p=0.5755); thus, there was no increase in other types of hospitalizations in the treatment group and there is a trend towards reduction of all cause hospitalizations.

Table 42. Summary of CEC Hospitalization Adjudications

	Treatment hospitalizations (6-month rate)	Control hospitalizations (6-month rate)	NBR p-value
6 Months			
All Cause Hospitalizations	232 (0.88)	263 (0.96)	0.4065
HF Hospitalizations	84 (0.32)	120 (0.44)	0.0002
Non-HF Hospitalizations	148 (0.56)	143 (0.52)	0.5755

All hospitalizations and their CEC adjudications are summarized in Table 43. Patients were hospitalized for a variety of reasons but there were no differences between the treatment and control groups, apart from HF hospitalizations. Thus, use of the Champion HF Monitoring System significantly reduced the number of HF hospitalizations with a neutral effect on non-HF hospitalizations.

Table 43. CEC Adjudication of Hospitalizations: Up to 6 Month Follow-up Visit

	TREATMENT (270)		CONTROL (280)	
	Subjects	Events	Subjects	Events
All Patients with a Hospitalization	118 (43.7%)	232	139 (49.6%)	263
Worsening Heart Failure at time of admission	55 (20.4%)	84	80 (28.6%)	120
Hypervolemic	43	63	71	100
Low output	16	20	16	20
Other	1	1	0	0
Cardiac hospitalization	50 (18.5%)	67	45 (16.1%)	57
Cardiac procedure	19	20	16	17
Complications of heart failure therapies	15	18	10	10
Ischemia	10	13	10	11
Arrhythmias	8	8	8	12
Syncope	1	1	2	2
Cardiac - Other	7	7	5	5
Vascular hospitalization	6 (2.2%)	6	7 (2.5%)	7
Stroke	1	1	3	3
Vascular surgery/procedure	1	1	2	2
Peripheral vascular disease	1	1	2	2
Vascular embolism	1	1	0	0
TIA	1	1	0	0
Other	1	1	0	0
Non-cardiac/vascular hospitalization	57 (21.1%)	75	58 (20.7%)	79
Infections and infestations	17	19	14	20
Gastrointestinal disorders	8	8	9	9
General disorders and administration site conditions	9	9	4	4
Metabolism and nutrition disorders	8	8	4	6
Respiratory, thoracic and mediastinal disorders	5	6	6	8
Surgical and medical procedures	5	5	6	6
Injury, poisoning and procedural complications	4	4	5	5
Musculoskeletal and connective tissue disorders	3	3	5	6
Nervous system disorders	4	4	3	3
Renal and urinary disorders	3	3	2	2
Blood and lymphatic system disorders	1	2	2	2
Hepatobiliary disorders	0	0	3	3
Psychiatric disorders	2	2	1	1
Investigations	2	2	0	0
Endocrine disorders	0	0	1	1
Neoplasms benign, malignant and unspecified	0	0	1	2
Social circumstances	0	0	1	1

10.9.4 All Cause Hospitalizations over Study Duration

The analysis in Table 44 below summarizes all the hospitalizations that occurred over the study duration, separated into heart failure and non-heart failure hospitalizations.

The same pattern seen in the analysis of the 6 month period was observed in the analysis over the full study duration. There was a reduction in HF hospitalizations in the treatment group compared to the control group (158 vs. 254) but there was no increase in non-HF

hospitalizations (338 vs. 343), again confirming the lack of an offsetting increase in other types of hospitalizations with a trend toward reduction in all cause hospitalizations.

Table 44. Summary of CEC Hospitalization Adjudications

Study Duration	Treatment hospitalizations (annualized rate)	Control hospitalizations (annualized rate)	NBR p-value
All Cause Hospitalizations	496 (1.44)	597 (1.71)	0.3320
HF Hospitalizations	158 (0.46)	254 (0.73)	<0.0001
Non-HF Hospitalizations	338 (0.98)	343 (0.98)	0.8415

Table 45 below summarizes all hospitalizations and their CEC adjudications over the study duration. The same pattern observed in the 6 month analysis was observed again with the treatment group demonstrating a reduction in HF hospitalizations but showing a neutral effect on non-HF hospitalizations.

Table 45. CEC Adjudication of Hospitalizations: Study Duration

	TREATMENT (270)		CONTROL (280)	
	Subjects	Events	Subjects	Events
All Patients with a Hospitalization	183 (67.8%)	496	198 (70.7%)	597
Worsening Heart Failure at time of admission	91 (33.7%)	158	116 (41.4%)	254
Hypervolemic	71	117	101	206
Low output	29	37	36	45
Other	3	4	3	3
Cardiac hospitalization	96 (35.6%)	161	84 (30.0%)	128
Cardiac procedure	41	53	33	38
Complications of heart failure therapies	30	38	21	23
Ischemia	17	22	16	25
Arrhythmias	23	27	19	27
Syncope	3	3	3	3
Cardiac - Other	15	18	12	12
Vascular hospitalization	14 (5.2%)	15	15 (5.4%)	18
Stroke	3	3	8	10
Vascular surgery/procedure	4	4	5	5
Peripheral vascular disease	2	2	2	2
Vascular embolism	2	2	0	0
TIA	1	1	1	1
Other	3	3	0	0
Non-cardiac/vascular hospitalization	103 (38.1%)	162	107 (38.2%)	197
Infections and infestations	38	43	43	59
Gastrointestinal disorders	18	20	22	26
Respiratory, thoracic and mediastinal disorders	10	12	19	30
Surgical and medical procedures	13	14	13	14

	TREATMENT (270)		CONTROL (280)	
	Subjects	Events	Subjects	Events
General disorders and administration site conditions	16	16	5	6
Metabolism and nutrition disorders	10	10	10	18
Musculoskeletal and connective tissue disorders	8	8	10	11
Injury, poisoning and procedural complications	9	9	8	8
Nervous system disorders	5	5	5	5
Renal and urinary disorders	5	5	4	4
Blood and lymphatic system disorders	3	4	4	4
Hepatobiliary disorders	3	3	3	3
Psychiatric disorders	5	5	1	1
Neoplasms benign, malignant and unspecified	4	4	1	2
Investigations	3	3	0	0
Endocrine disorders	0	0	2	2
Ear and labyrinth disorders	0	0	1	1
Eye disorders	1	1	0	0
Immune system disorders	0	0	1	1
Skin and subcutaneous tissue disorders	0	0	1	1
Social circumstances	0	0	1	1

10.9.5 HF Hospitalizations with Covariates

Table 46 summarizes the supplementary analysis of HF hospitalizations over the full study duration that included an adjustment for covariates. It is worth noting that there were no statistically significant differences in baseline characteristics between the treatment and control groups. Nonetheless, it is known that many factors can influence the rate of hospitalization among HF patients. The backward elimination procedure entered the following pre-specified variables, known to be related to HF hospitalization, into the model: age, sex, race, atrial flutter/fibrillation, BMI, cardiac index, cardiac output, creatinine, blood urea nitrogen (BUN), diabetes, ACEI/ARB use, heart rate, beta blocker dose, glomerular filtration rate (GFR), pulmonary vascular resistance (PVR), blood pressure, time from qualifying hospitalization (<60 days vs. ≥ 60 days), Minnesota Living with Heart Failure Questionnaire and ejection fraction. The final NBR model included the following covariates: age, diabetes, atrial flutter/fibrillation, gender, heart rate, glomerular filtration rate (GFR), pulmonary vascular resistance (PVR), Minnesota Living with Heart Failure Questionnaire and beta blocker dose. The final A-G model included the following covariates: age, diabetes, atrial flutter/fibrillation, BUN, ACEI/ARB use, BMI, cardiac index, PVR, creatinine, gender, GFR, Minnesota Living with Heart Failure Questionnaire and beta blocker dose. When analyzing the rate of HF hospitalizations, the treatment group rate was significantly lower than the control group rate, using either the negative binomial regression model ($p=0.0007$) or the Anderson Gill model ($p<0.0001$), again confirming the robustness of the primary endpoint. Therefore, the inclusion of covariates in the model resulted in minimal change to the statistical significance of the unadjusted model.

Table 46. Supplementary Analyses of Rate of Heart Failure Hospitalizations with Covariates – Study Duration

	TREATMENT (270)		CONTROL (280)		ALL PATIENTS (550)			
	# Hosp.	**Hosp. Rate** (events/ patient-year)	**# Hosp.**	**Hosp. Rate** (events/ patient-year)	**NBR p-value[1]**	**RRR**	**NNT**	**A-G p-value[2] / Hazard Ratio (95% CI)**
Entire Blinded Randomized Follow-Up	158	0.46	254	0.73	0.0007	37%	4	<0.0001 / 0.60 (0.49-0.75)

[1] p-value from the negative binomial regression (NBR) model with covariates selected using backward elimination technique.
[2] p-value / Hazard ratio (Treatment to Control) and 95% Confidence Interval from the Andersen-Gill (A-G) model with covariates selected using backward elimination technique.
NNT = Number needed to treat, RRR = Relative Risk Reduction

10.9.6 Outcomes According to Gender

The CHAMPION Trial was neither designed nor powered to evaluate the primary efficacy endpoint in subgroups such as gender. The treatment group provides a significant benefit over the control group when stratified for gender. Although gender was a significant predictor of risk of HF hospitalization or death in the Cox regression model, this was influenced by the disproportionate number of female control patient deaths (7 control deaths vs. 3 treatment deaths, HR=0.41, p=0.187). Thus, the women in the control group most likely to have HF hospitalizations had a reduced duration in the study and reduced contribution to the primary endpoint.

Ancillary Analyses of Heart Failure Hospitalizations with Gender

6-Month Results

A stratified Andersen-Gill model analyzes multiple hospitalizations while stratifying based on baseline characteristics. The analyses of 6 month HF hospitalizations stratified for gender is provided below. The treatment group provides significant benefit over the control group (p = 0.0240, Hazard Ratio = 0.725) while stratifying based on gender (Table 47).

Table 47. HF Hospitalizations at 6 Months Stratified on Gender

	Treatment			Control		
	Subjects	**# 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
Stratified Andersen-Gill p-value = 0.0240, HR [95% CI] = 0.725 [0.549, 0.959]						

Full Study Duration Results

The analysis of HF hospitalizations over the full study duration was performed stratifying on gender (Table 48). The treatment group provides significant benefit over the control group (p <0.0001, Hazard Ratio = 0.634) while stratifying for gender.

Table 48. HF Hospitalizations over Full 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
Stratified Andersen-Gill p-value < 0.0001, HR [95% CI] = 0.634 [0.520, 0.773]						

Ancillary Analyses of 6 Month Heart Failure Hospitalization or Death with Gender as Exploratory Variables

Compared to the treatment group, more than twice as many women in the control died within 6 months (7 control deaths vs. 3 treatment deaths, HR = 0.41, p=0.187). Since patients at greatest risk of dying also have increased risk for HF hospitalization, it is important to also analyze gender using HF hospitalization or death as the outcome. These analyses show that the treatment effect remains significant, after adjustments for gender and other subgroup factors.

These analyses differ from the previous analyses in the following aspects:

1. The outcome variable was the occurrence of either a HF hospitalization or death within 6 months. This was motivated by the fact that relative HF hospitalization rates are difficult to interpret in the presence of mortality disparities in gender.
2. Gender, along with an expanded list of possible covariates, was included in a standard Cox regression model. The entire list of variables consisted of: age, gender, race, BMI, systolic BP, heart rate, creatinine, GFR, BUN, CRT/CRT-D, etiology of cardiomyopathy, cardiac output, ejection fraction, atrial fibrillation, diabetes, on ACE/ARB, beta blocker dose, cardiac index, and PVR.
3. Forward and backward stepwise procedures were used and included interaction variables for *gender by randomization_group*.

Both the forward and backward approaches had similar findings. The results of the backward stepwise regression for a HF hospitalization or death within 6 months are displayed in Table 49. The treatment group continued to show significant benefit over the control group (p = 0.013) after adjustment for gender and other covariates remaining in the stepwise regression models.

Table 49. HF Hospitalization or Death (Backward Stepwise Cox Regression Procedure)

Baseline Predictors Remaining in the Model		**Main Effects**	
	Adjusted p-value		p-value
Age	**.011**	Gender	**.001**
Heart Rate	**.011**		
Screening GFR	**.000**		
Beta blocker dose	**.010**	**Interactions**	
PVR	**.000**		p-value
Gender	**.001**	Treatment x Gender	0.940
TREATMENT	**.013**		

Results from Cox Regression.

Randomization group interactions with gender were not significant in either model. This analysis further supports the robustness of the treatment effect in gender after adjusting for the potential contribution of baseline factors.

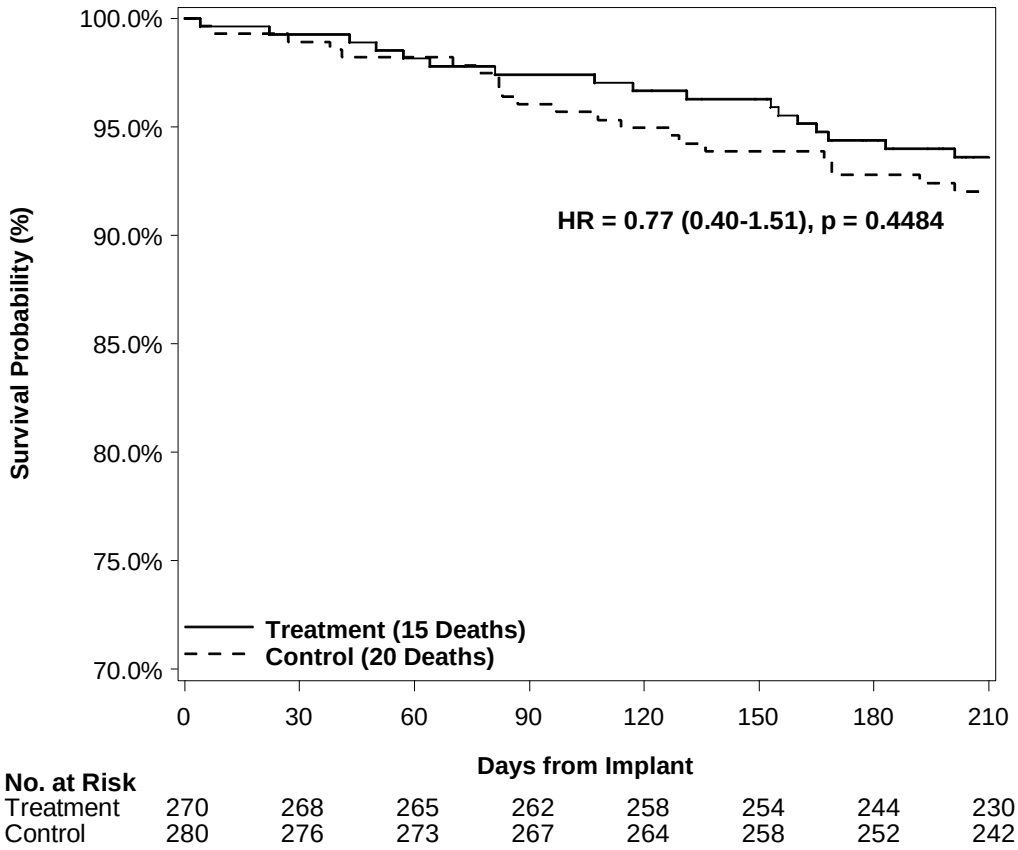
10.10 Survival Analyses

10.10.1 Patient Survival up to 6 Months

Survival Analysis

There were 15 deaths among 270 treatment patients and 20 deaths among 280 control patients up to the 6 month follow-up visit. The treatment group trended towards improved survival (HR 0.77, 95% CI 0.40 – 1.5, p=0.4484) (Figure 17).

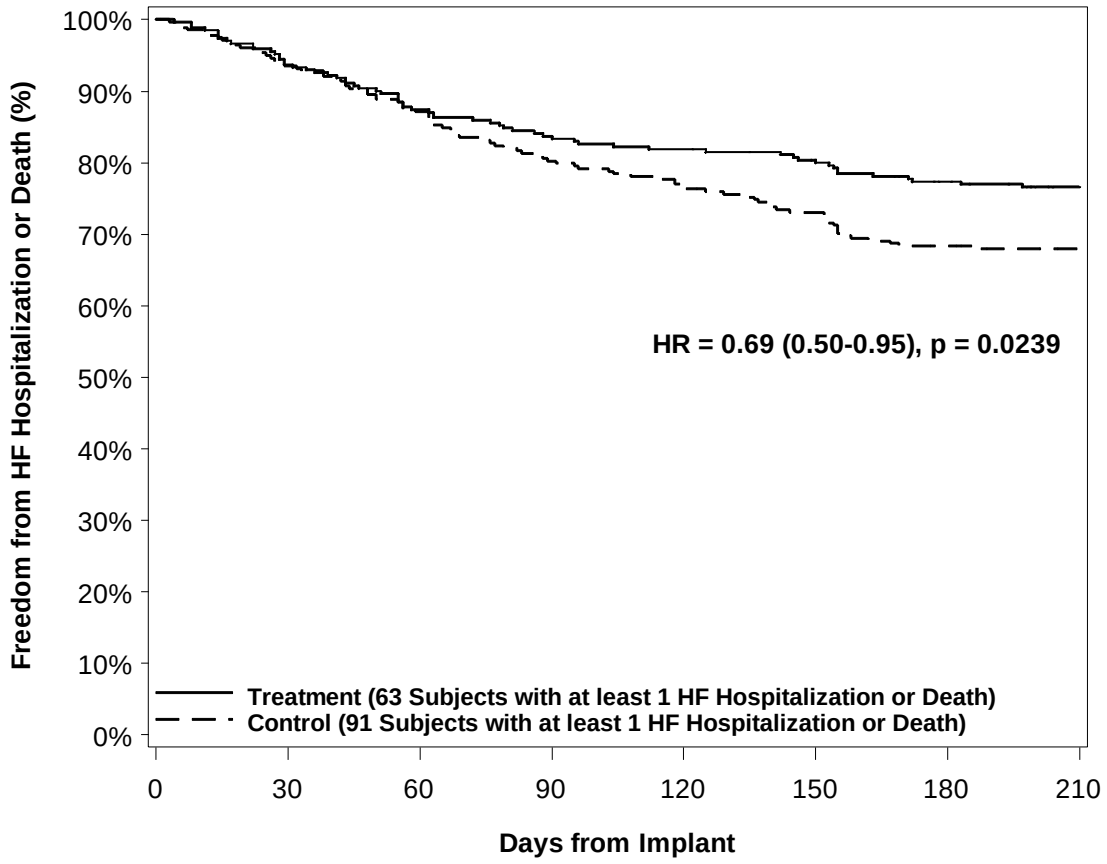
Figure 17. Kaplan-Meier Patient Survival Plot up to 6 Months



HF Hospitalization-Free Survival Analysis

At 6 months, the treatment group had significantly increased survival without HF hospitalizations compared to the control group with a hazard ratio of treatment to control of 0.69 (95% CI 0.50 – 0.95; p=0.0239) (Figure 18).

Figure 18. Freedom from HF Hospitalization or Death at 6 Months



No. at Risk								
Treatment	270	253	236	225	221	213	201	186
Control	280	261	242	223	212	202	186	177

The CEC adjudications of mortality indicate that the major causes of death were related to cardiac disease (Table 50).

Table 50. 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

10.10.2 Patient Survival over the Study Duration

Survival Analysis

There was no difference in survival between the treatment and control groups over study duration (Figure 19).

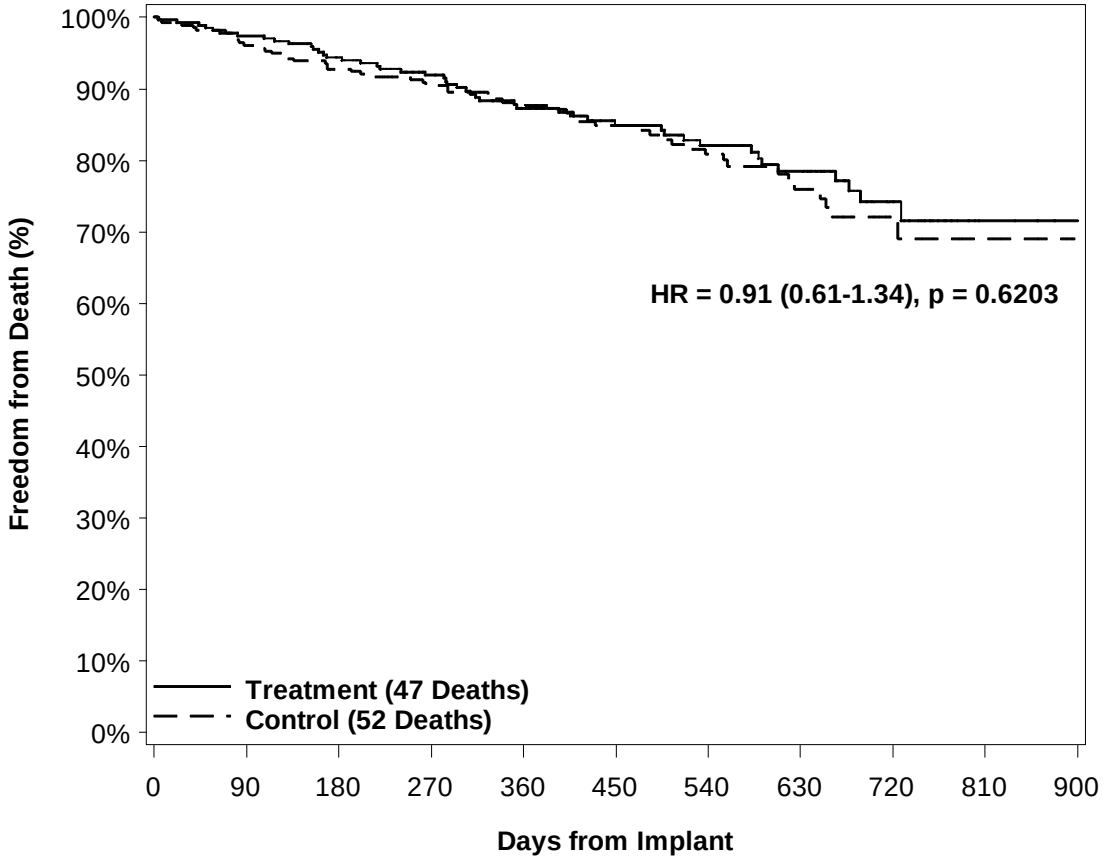
Table 51 provides the CEC Adjudication of mortality over the study duration.

Table 51. CEC Adjudication of Mortality over the Study Duration

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)
Total Subjects with Mortality	47 (17.4%)	52 (18.5%)	99 (18.0%)
Cause of Death			
Heart Failure	20 (7.4%)	20 (7.1%)	40 (7.3%)
Sudden Cardiac Death	13 (4.8%)	13 (4.6%)	26 (4.7%)
Cardiac Procedure	4 (1.5%)	2 (0.7%)	6 (1.1%)
Myocardial Infarction	1 (0.4%)	1 (0.4%)	2 (0.4%)
Cardiac-Other [1]	0 (0.0%)	2 (0.7%)	2 (0.4%)
Stroke	0 (0.0%)	1 (0.4%)	1 (0.2%)
Subdural hematoma	2 (0.7%)	0 (0.0%)	2 (0.4%)
Non-cardiac/Non-vascular	7 (2.6%)	13 (4.6%)	20 (3.6%)

[1] Non-ischemic ventricular dysrhythmia and heart transplant rejection

Figure 19. Kaplan-Meier Patient Survival Plot Over the Study Duration

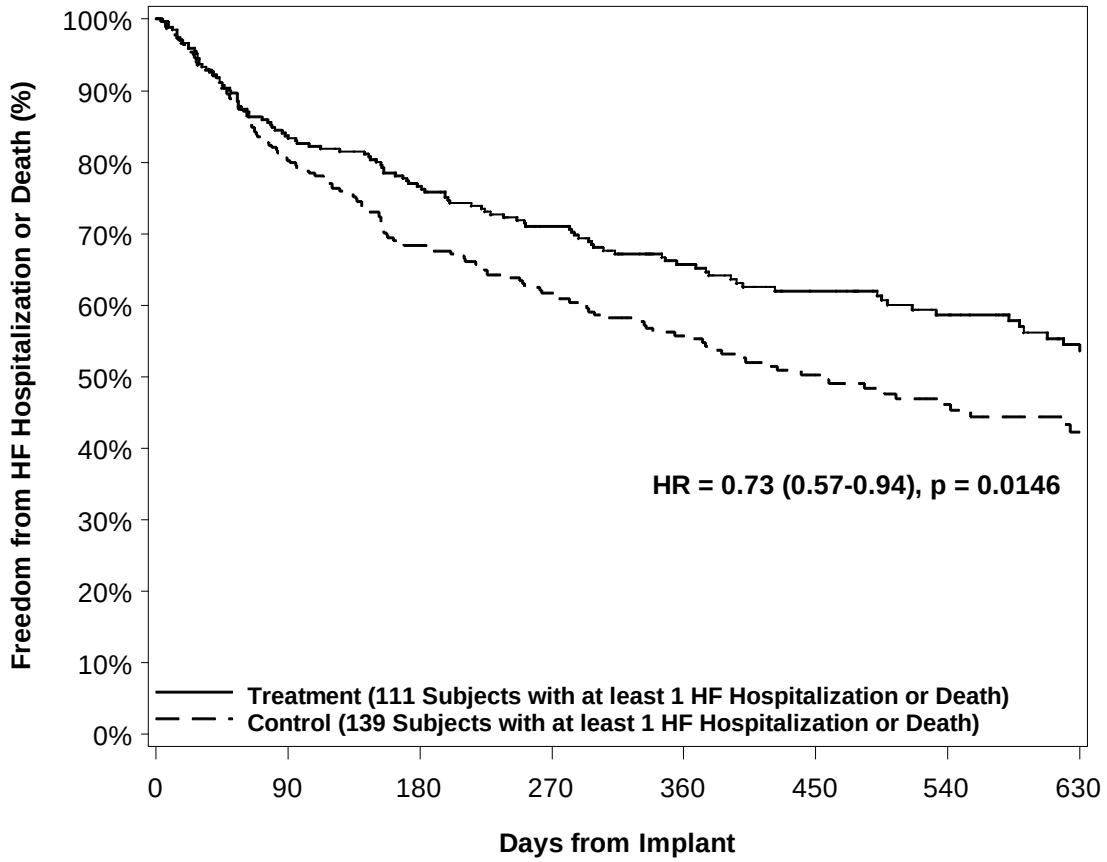


No. at Risk											
Treatment	270	262	244	210	169	131	108	82	29	5	1
Control	280	267	252	215	179	137	105	67	25	10	0

HF Hospitalization-Free Survival Analysis

Figure 20 summarizes the composite endpoint of time to first HF hospitalization or death over the study duration. As expected, because of the nearly overlapping survival curves, the composite endpoint is based largely on the differences in HF hospitalizations. Overall, there were 111 treatment patients vs. 139 control patients with composite events. The hazard ratio was 0.73 (95% CI 0.57-0.94; p=0.0146) demonstrating a significant benefit for subjects in the treatment group in reducing the time to death or first HF hospitalization.

Figure 20. Freedom from HF Hospitalization or Death Over the Study Duration

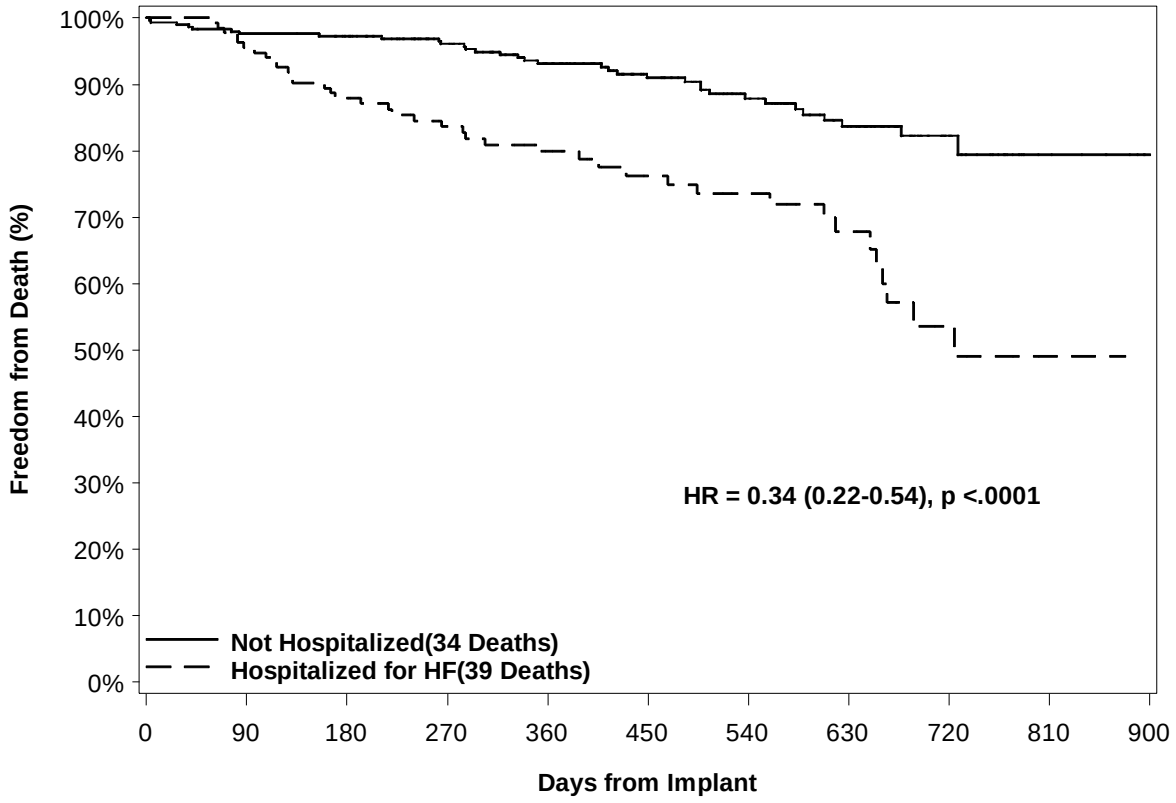


No. at Risk								
Treatment	270	225	201	168	130	104	83	62
Control	280	223	186	145	112	79	56	38

10.10.3 Survival in Subjects Hospitalized for HF versus Non-Hospitalized Subjects

Patients hospitalized for HF within 6 months of enrollment had significantly decreased survival compared to patients who were never hospitalized (Figure 21).

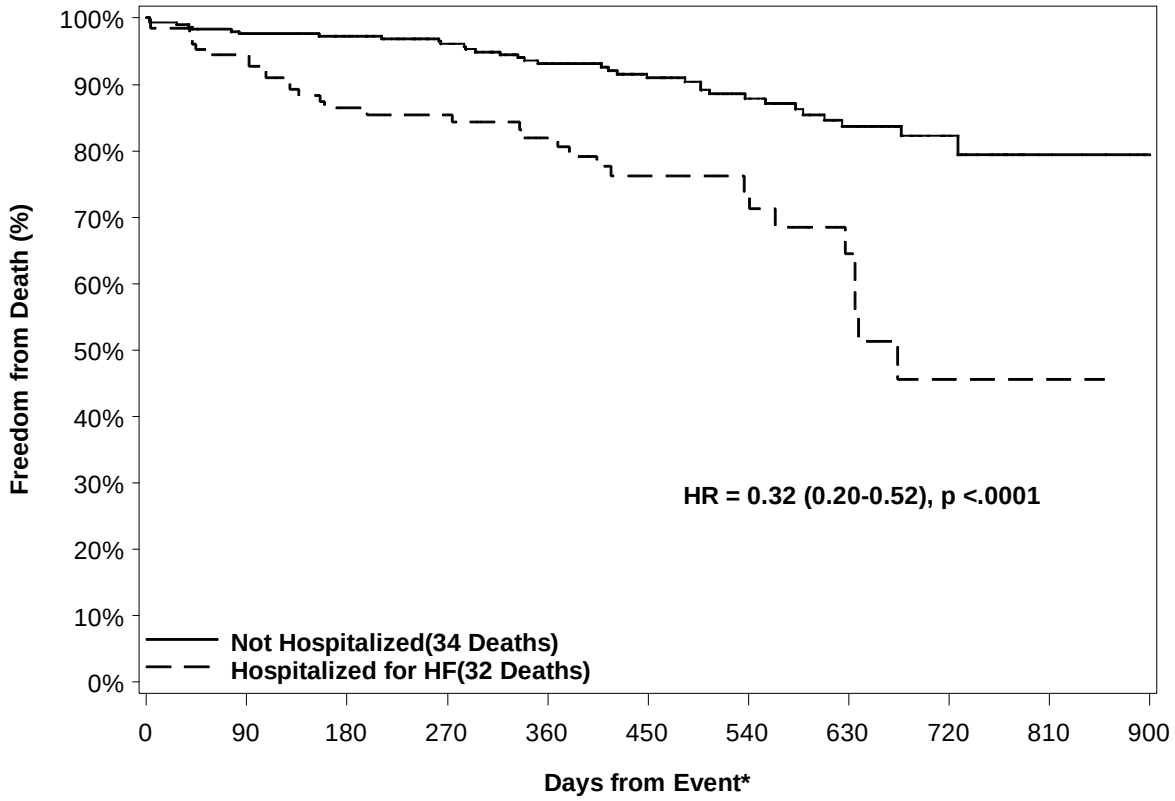
Figure 21. Survival in Patients Not Hospitalized vs. Patients Hospitalized for HF



No. at Risk											
Not Hospitalized	293	284	278	244	199	161	126	93	31	10	1
Hospitalized	135	128	112	94	79	57	49	29	13	2	0

Figure 22 shows the Kaplan-Meier probability of death after the first HF hospitalization compared to patients who are not hospitalized within the first 6 months. This plot is different from Figure 21 in that it does not include 7 patients who died during a HF hospitalization. Following discharge, patients who are hospitalized have a much lower survival compared to patients who are not hospitalized. This demonstrates the value of preventing not just the index hospitalizations but also subsequent hospitalizations, i.e. the risk of death remains increased even after surviving the first HF hospitalization. Thus, prevention of HF hospitalizations is a key part of reducing mortality from HF and the primary endpoint of the CHAMPION trial which measures all HF hospitalizations appears to be particularly relevant.

Figure 22. Survival in Patients Not Hospitalized vs. Patients Following Discharge from HF Hospitalization



No. at Risk											
Not Hospitalized	293	284	278	244	199	161	126	93	31	10	1
Hospitalized	128	113	87	78	63	46	29	15	6	1	0

*Patients not hospitalized for HF are measured for survival from implant date, and hospitalized patients are measured from HF hospitalization discharge date

10.11 Adverse Events

10.11.1 Adverse Events up to 6 Months

An adverse event (AE) was defined as any unfavorable and unintended sign, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure that occurs during the course of the study. An Adverse Event was defined in the protocol as being independent of assumption of any causality (e.g., primary or concomitant disease or study design). Table 52 contains a summary of the patients who had adverse events during the trial.

Table 52. Overall Summary of Adverse Events Up to 6 Month Follow-up Visit

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)
Adverse Events			
Serious Adverse Events			
Subjects	121 (44.8%)	155 (55.4%)	276 (50.2%)
Events	339	385	724
Procedure Related			
Subjects	3 (1.1%)	4 (1.4%)	7 (1.3%)
Events	3	4	7
Non-Serious Adverse Events			
Subjects	175 (64.8%)	174 (62.1%)	349 (63.5%)
Events	603	505	1108
Anticipated Adverse Events			
Anticipated Adverse Events			
Subjects	38 (14.1%)	31 (11.1%)	69 (12.5%)
Events	47	34	81
Anticipated Serious Adverse Events			
Subjects	0 (0.0%)	0 (0.0%)	0 (0.0%)
Events	0	0	0
Adverse Device Events			
Unanticipated Serious Adverse Device Events			
Subjects	0 (0.0%)	1 (0.4%)	1 (0.2%)
Events	0	1	1
Serious Adverse Device Events			
Subjects	2 (0.7%)	0 (0.0%)	2 (0.4%)
Events	2	0	2
Non-Serious Adverse Device Events			
Subjects	5 (1.9%)	7 (2.5%)	12 (2.2%)
Events	6	11	17

Serious and Non-serious Adverse Events

Serious Adverse Events

For this study, a Serious Adverse Events was defined by the investigator as any untoward medical occurrence that:

• resulted in death
• was immediately life-threatening
• required hospitalization > 24 hours or prolonged an existing hospitalization
• resulted in disability/incapacity
• resulted in a congenital anomaly/birth defect
• required intervention to prevent one of the above

All serious adverse events were adjudicated by the CEC. The number of serious adverse events was lower in the treatment group prior to 6 months (Table 53).

Table 53. Serious Adverse Events up to 6 Months

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)
Serious Adverse Events up to 6 Months			
Subjects	121 (44.8%)	155 (55.4%)	276 (50.2%)
Events	339	385	724

CEC Adjudicated Procedure Related Adverse Events

Table 54 lists the 7 SAEs that were adjudicated as procedure related by the CEC. In 6 cases, the patient recovered without any sequela. One patient, who underwent a successful implant and was ready for discharge, developed hypotension and cardiogenic shock. He recovered, was released on home inotropes, and ultimately received a heart transplant.

Table 54. Procedure Related Adverse Events – CEC adjudication

Procedure Related	Description	Treatment	Outcome
Atrial fibrillation	History of Atrial Fibrillation. One day post-procedure developed rapid Atrial Fibrillation.	• Ibutilide 1 mg IV • TEE with successful cardioversion	• Recovered without sequela
Cardiogenic Shock	One day post-procedure patient became symptomatically hypotensive	• Inotropes • IABP	• Home inotropes • Listed for Heart Transplant
Fever	Approximately 6 hours after the implant procedure, the patient developed a fever of 100.6, with a temperature max of 101.2.	• Blood cultures negative • No treatment rendered	• Fever resolved without intervention • Recovered without sequela
Groin Hematoma	One day post-procedure, oozing was noted at the cath site. Physical inspection was negative for a hematoma however the cath site did have a steady ooze.	• Right groin was injected with 3 cc lidocaine/epinephrine • Pressure dressing and manual pressure was applied for 20 minutes.	• Recovered without sequela
Groin pain	Following the implant procedure, the patient complained of right groin pain.	• Discharge postponed in order to observe patient for an additional day.	• Recovered without sequela
Hemoptysis	Patient developed mild hemoptysis during the procedure	• Observed post procedure with no significant pulmonary abnormalities developing on	• Hemoptysis resolved without intervention

		chest x-ray	• Recovered without sequela
Stopped Coumadin for implant	INR remained subtherapeutic after implant and re-initiation of Coumadin	• Patient remained hospitalized until INR therapeutic due to history of mechanical valve	• Recovered without sequela

Non-serious Adverse Events

An adverse event (AE) is defined as any unfavorable and unintended sign, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure that occurs during the course of the study. An Adverse Event was defined in the protocol as being independent of assumption of any causality (e.g., primary or concomitant disease or study design).

Non-serious adverse events were site reported and not adjudicated by the CEC. The number of non-serious adverse events was similar in both groups prior to 6 months (Table 55). The non-serious events were typical for heart failure trials with a non-significant difference between the two groups at 6 months (p = 0.0987).

Table 55. Non-serious Adverse Events

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)
Non-Serious Adverse Events up to 6 Months			
Subjects	175 (64.8%)	174 (62.1%)	349 (63.5%)
Events	603	505	1108
Non-significant differences in number of events between treatment and control at 6 months (p = 0.0987) using Wilcoxon rank sum test			

Anticipated Adverse Events

Anticipated Adverse Events were defined in the protocol as adverse events associated with the sensor implant procedure (including the RHC) or post-implant complications that included the following: air embolism, abnormal heart beats or heart rate, bleeding, delayed wound healing, infection, hematoma, thrombus (blood clot) formation at catheter insertion site, venous trauma (e.g., perforation, dissection), and valve damage.

The following table reports all anticipated adverse events occurring within 30 days of implant regardless of causality to the implant and therefore using the broadest definition possible. These events (Table 56) were infrequent and within ranges expected with invasive right heart catheterization procedures performed in patients with advanced NYHA Class III heart failure, as evidenced in the published results from the ESCAPE trial (Binanay, et al., 2005). The events included infection (28 events in 26 patients), arrhythmias (25 events in 23 patients), bleeding (19 events in 18 patients), hematoma (7 events in 7 patients) and thrombus (2 events in 2 patients. There were no differences in the percent of patients or the number of events occurring between the treatment and control groups.

Table 56. Anticipated Adverse Events

	TREATMENT (270)		CONTROL (280)		ALL PATIENTS (550)	
	Subjects	Events	Subjects	Events	Subjects	Events
All Patients with an Event	38 (14.1%)	47	31 (11.1%)	34	69 (12.5%)	81
Infection	14 (5.2%)	16	12 (4.3%)	12	26 (4.7%)	28
Upper respiratory infection	3	3	2	2	5	5
Urinary tract infection	3	3	2	2	5	5
Bronchitis	1	1	3	3	4	4
Pneumonia	2	2	1	1	3	3
Cold	2	2	0	0	2	2
Influenza	2	2	0	0	2	2
Acute bronchitis	0	0	1	1	1	1
Aspiration pneumonia	1	1	0	0	1	1
Groin abscess	0	0	1	1	1	1
Methicillin-resistant staphylococcal aureus infection	1	1	0	0	1	1
Pulmonary infiltration	1	1	0	0	1	1
Sinusitis	0	0	1	1	1	1
UTI	0	0	1	1	1	1
Arrhythmias	14 (5.2%)	16	9 (3.2%)	9	23 (4.2%)	25
Ventricular tachycardia	5	5	4	4	9	9
Atrial fibrillation	5	5	2	2	7	7
Ventricular arrhythmia	2	2	0	0	2	2
Ventricular fibrillation	1	1	1	1	2	2
Atrial fibrillation with rapid ventricular response	1	1	0	0	1	1
Atrial flutter	0	0	1	1	1	1
Cardiac dysrhythmias	1	1	0	0	1	1
Tachycardia	1	1	0	0	1	1
Wide complex tachycardia	0	0	1	1	1	1
Bleeding	9 (3.3%)	9	9 (3.2%)	10	18 (3.3%)	19
Epistaxis	3	3	2	2	5	5
Hemoptysis	3	3	2	2	5	5
GI bleed	2	2	1	1	3	3
Bleeding	1	1	0	0	1	1
Blood in stool	0	0	1	1	1	1
Catheter site bleeding	0	0	1	1	1	1
Catheter site ecchymosis	0	0	1	1	1	1
Hematuria	0	0	1	1	1	1
Nose bleeds	0	0	1	1	1	1
Haematoma	4 (1.5%)	4	3 (1.1%)	3	7 (1.3%)	7
Hematoma	2	2	2	2	4	4
Catheter site hematoma	1	1	1	1	2	2
Vessel puncture site hematoma	1	1	0	0	1	1
Thrombus	2 (0.7%)	2	0 (0.0%)	0	2 (0.4%)	2
Arterial thrombosis (limbs)	1	1	0	0	1	1
Clot blood	1	1	0	0	1	1

Bleeding

There were 24 patients with 26 events who experienced a bleeding event within 30 days of implant; bleeding (19 events in 18 patients), hematoma (7 events in 7 patients). Of these 26 events, 21 were minor bleeding events such as epistaxis, hematuria, hematochezia, etc.

Five of the 26 events were major bleeding events defined as requiring transfusion. Of these, 2 patients experienced GI bleeding; 2 patients experienced hemoptysis; 1 patient experienced a groin hematoma. None of these events resulted in death; 1 patient required partial gastrectomy for chronic ulcer disease. Two of these patients were on ASA and clopidogrel and 3 were continued on previously indicated warfarin.

The overall risk of major bleeding within 30 days of implant was 0.9% (5/550). For patients on warfarin therapy there was a 1.4% risk of major bleeding (3/213). For patients on ASA/clopidogrel there was a 0.6% risk of major bleeding (2/319). Reported risk of major bleeding with warfarin therapy ranges between 0.6 to 2.7 % (Coumadin package insert). The reported risk of major bleeding with dual antiplatelet therapy of ASA and clopidogrel was 0.6% in COMMIT, a clinical trial with a dosing regimen similar to CHAMPION (Chen, et al., 2005). Thus, the risk of bleeding in this trial is similar to reported event rates for warfarin or clopidogrel. Per recommendations from the DSMB, the protocol was amended to suggest proton pump inhibitor for patients at risk for GI bleeding during the period in which dual antiplatelet therapy was given.

Anticipated Serious Adverse Events

Anticipated Serious Adverse Events were defined in the protocol as associated with the implant procedure (including the RHC) or post-implant complications including pulmonary infarct or pulmonary embolism.

No Anticipated Serious Adverse Events occurred in the trial during the 6 month follow-up period.

Adverse Device Events

Unanticipated Serious Adverse Device Events

An unanticipated adverse device event was defined as any serious adverse effect on health or safety or life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or

application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

Unanticipated serious adverse device events (Table 57) were rare during the trial. The only event was a tingling sensation in one control patient which resolved spontaneously and did not require any treatment. During a routine office visit, the patient described what he thought to be a shock and "tingling sensation" from his home unit. He stated he was not harmed and physical exam revealed no signs of electric shock. The patient continued to take readings from his home unit. A replacement home unit was sent to the patient and he used the replacement unit without difficulty. The home unit in question was returned to CardioMEMS, and an examination of the electronics unit found that there was no malfunction of the device or failure of the isolation between the power supply and the patient.

The Clinical Events Committee reviewed the event on June 27, 2009. The committee determined the event was not serious and not device/system related.

Table 57. Unanticipated Serious Adverse Device Events

	TREATMENT (270)		CONTROL (280)		ALL PATIENTS (550)	
	Subjects	Events	Subjects	Events	Subjects	Events
All Patients with an Event	0 (0.0%)	0	1 (0.4%)	1	1 (0.2%)	1
Nervous System Disorder	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (100.0%)	1 (0.2%)	1 (100.0%)
Tingling Sensation	0	0	1	1	1	1

Serious Adverse Device Events

A Serious Adverse Device Event (SADE) was defined in the protocol as an event that meets any of the criteria for a Serious Adverse Event and is considered possibly or definitely related to the device or the insertion procedure by the investigator.

There were two SADE reported by the investigators during the 6 month follow-up period as shown in Table 58. These events were adjudicated by the CEC as being device/system related (DSRC).

Table 58. Serious Adverse Device Events Up to 6 Month Follow-up Visit

	TREATMENT (270)		CONTROL (280)		ALL PATIENTS (550)	
	Subjects	Events	Subjects	Events	Subjects	Events
All Patients with an Event	2 (0.7%)	2	0 (0.0%)	0	2 (0.4%)	2
Respiratory, thoracic and mediastinal disorders	1 (0.4%)	1 (50.0%)			1 (0.2%)	1 (50.0%)
Hemoptysis	1	1	0	0	1	1

	TREATMENT (270)		CONTROL (280)		ALL PATIENTS (550)	
	Subjects	Events	Subjects	Events	Subjects	Events
Vascular disorders	1 (0.4%)	1 (50.0%)			1 (0.2%)	1 (50.0%)
Blood clot	1	1	0	0	1	1

Hemoptysis occurred in a patient on chronic anti-coagulation and history of chronic bronchitis. The patient had severe coughing and during the RHC and subsequently developed hemoptysis. Pulmonary angiography did not reveal perforation or extravasation. After intubation, bronchoscopy demonstrated old blood in both mainstem bronchi; cultures grew Klebsiella. He was treated with anti-biotics and made a full recovery.

The Swan Ganz balloon was over inflated in a small pulmonary artery branch resulting in a small dissection and non-occlusive thrombus. The patient was treated with heparin and Coumadin and did not suffer pulmonary infarction or other clinical sequelae.

Non-Serious Adverse Device Events

An Adverse Device Event (ADE) was any undesirable clinical event in a subject considered possibly or definitely related to the device or the insertion procedure by the investigator. An ADE could occur at any time after exposure to the Investigational Device. Adverse events classified as non-serious and related to the device occurring up to 6 months are presented in Table 59. These events were rare and are well known adverse events for right heart catheterization procedures. There were no significant differences between the treatment and control groups.

Table 59. Non-Serious Adverse Device Events Up to 6 Month Follow-up Visit

	TREATMENT (270)		CONTROL (280)		ALL PATIENTS (550)	
	Subjects	Events	Subjects	Events	Subjects	Events
All Patients with an Event	5 (1.9%)	6	7 (2.5%)	11	12 (2.2%)	17
General disorders and administration site conditions	1 (0.4%)	1 (16.7%)	4 (1.4%)	6 (54.5%)	5 (0.9%)	7 (41.2%)
Catheter site bleeding	0	0	1	1	1	1
Catheter site ecchymosis	0	0	1	1	1	1
Catheter site hematoma	0	0	1	1	1	1
Chest discomfort	0	0	1	1	1	1
Chest pain	0	0	1	1	1	1
Non-cardiac chest pain	1	1	0	0	1	1
Vessel puncture site pain	0	0	1	1	1	1
Investigations	2 (0.7%)	2 (33.3%)	1 (0.4%)	1 (9.1%)	3 (0.5%)	3 (17.6%)
Cardiac monitoring abnormal	1	1	0	0	1	1
Heart rate irregular	0	0	1	1	1	1
Serum creatinine increased	1	1	0	0	1	1
Respiratory, thoracic and mediastinal disorders	2 (0.7%)	2 (33.3%)	1 (0.4%)	1 (9.1%)	3 (0.5%)	3 (17.6%)
Hemoptysis	1	1	1	1	2	2
Dyspnea	1	1	0	0	1	1
Cardiac disorders	1 (0.4%)	1 (16.7%)	1 (0.4%)	1 (9.1%)	2 (0.4%)	2 (11.8%)
Congestive heart failure	1	1	0	0	1	1

	TREATMENT (270)		CONTROL (280)		ALL PATIENTS (550)	
	Subjects	Events	Subjects	Events	Subjects	Events
Ventricular tachycardia	0	0	1	1	1	1
Nervous system disorders	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (9.1%)	1 (0.2%)	1 (5.9%)
Dizziness	0	0	1	1	1	1
Vascular disorders	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (9.1%)	1 (0.2%)	1 (5.9%)
Vessel perforation	0	0	1	1	1	1

10.11.2 Adverse Events After 6 Month Follow-up Visit

Table 60 contains the summary of adverse events for the follow-up period after the 6 month visit. There were no unanticipated, serious, or non-serious adverse device events or anticipated adverse events after the 6 month visit follow-up period.

Table 60. Overall Summary of Adverse Events After 6 Month Follow-up Visit

	TREATMENT (244)	CONTROL (254)	ALL PATIENTS (498)
Serious Adverse Events			
Subjects	129 (52.9%)	137 (53.9%)	266 (53.4%)
Events	353	434	787
Non-Serious Adverse Events			
Subjects	128 (52.5%)	120 (47.2%)	248 (49.8%)
Events	414	379	793
Anticipated Serious Adverse Events			
Subjects	2 (0.8%)	0 (0.0%)	2 (0.4%)
Events	2	0	0

Serious and Non-serious Adverse Events

Serious Adverse Events

After 6 months, there were 353 serious adverse events in the treatment arm compared to 434 serious adverse events in the control arm. Over the study duration, there were 692 serious adverse events in the treatment arm and 819 serious adverse events in the control arm (Table 61). The difference of 127 less events in the treatment arm is predominately due to the number of reduced HF hospitalizations

Table 61. Serious Adverse Events after 6 Months

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)
Serious Adverse Events up to 6 Months			
Subjects	121 (44.8%)	155 (55.4%)	276 (50.2%)
Events	339	385	724
Serious Adverse Events after 6 Months			
Subjects	129 (52.9%)	137 (53.9%)	266 (53.4%)

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)
Events	353	434	787
Serious Adverse Events over Study Duration(6 Months plus after 6 months)			
Events	692	819	1511

Non-serious Adverse Events

Non-serious adverse events were site reported and not adjudicated by the CEC. The number of non-serious adverse events was similar in both groups after 6 months (Table 62). The non-serious events were typical for heart failure trials with a non-significant difference between the two groups after 6 months (p = 0.3543).

Table 62. Non-serious Adverse Events

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)
Non-Serious Adverse Events after 6 Months			
Subjects	128 (52.5%)	120 (47.2%)	248 (49.8%)
Events	414	379	793
Non-significant differences in number of events between treatment and control after 6 months (p = 0.3777) using Wilcoxon rank sum test.			

Anticipated Serious Adverse Events

Anticipated Serious Adverse Events were defined in the protocol as associated with the implant procedure (including the RHC) or post-implant complications including pulmonary infarct or pulmonary embolism.

There were two Anticipated Serious Adverse Events of pulmonary embolism that occurred after the 6 month follow-up period. Neither event was adjudicated by the Clinical Events Committee (CEC) as being device or system related.

10.12 Study Summary and Conclusion

Clinical Relevance

Although significant progress has been made in the treatment of HF over the past several decades, particularly in the reduction of mortality, HF hospitalizations (> 1 million /year, ~$ 40 billion in Medicare costs) remain a major clinical and public health problem.

Wireless hemodynamic monitoring in the CHAMPION Trial improved patient outcomes in a number of areas of which the most important was a reduction in heart failure hospitalizations. To provide clinical context for the findings of CHAMPION, we reviewed 10 landmark trials of device or pharmacologic interventions that established standard therapies for patients with heart failure (Appendix B - **Error! Reference source not found.**).

The annualized relative risk reduction (RRR) for heart failure hospitalization in the CHAMPION Trial of 37% and absolute risk reduction (ARR) of 0.27 compare favorably to the average HF hospitalization RRR of 25% ± 13% and ARR of 0.06 ± 0.09 in the comparison trials. Further, the number needed to treat (NNT) to prevent one hospitalization of 4 in CHAMPION is much lower than the average of 27 ± 20 in these trials. The improvement demonstrated in CHAMPION was incremental to the current standard of care, available to both study arms, which was informed by these prior trials.

Reduction in HF hospitalizations is considered to be one of the most important clinical benefits for patients with heart failure, since hospitalization rates and costs are extremely high for this patient population. Moreover, data from the CHAMPION trial and others consistently show that overall mortality rates increase following a HF hospitalization, leading to another benefit of treatments that prevent decompensation leading to hospitalizations.

The treatment group had significantly better survival without HF hospitalization at 6 months and over the full study duration. There was numerical superiority in survival for the treatment group at 6 months and over study duration.

In addition to reduced HF hospitalizations, QOL was improved in the treatment group, but, consistent with a positive overall impact on well-being, even patients who were never hospitalized had a better quality of life in the treatment group compared to the control group. This suggests that the benefit of hemodynamic management for patients goes beyond the reduction of hospitalizations.

Current healthcare initiatives call for clinical treatments that are cost effective and a cost effectiveness study was part of the CHAMPION Trial (Abraham, et al., 2011). Wireless hemodynamic monitoring was cost effective (ICER $13,979) and compared favorably to

other cardiovascular devices (ICERs $19,500 to $47,800, Appendix C - **Error! Reference source not found.**).

In summary, the wireless hemodynamic monitoring management system tested in the CHAMPION Trial offers a cost-effective clinically relevant benefit across a wide range of measures and compares favorably to improvements achieved with therapies now considered standard for heart failure.

Summary

Safety

- 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.

Efficacy

- The treatment group rate of HF hospitalizations was significantly reduced in comparison to the control group (0.32 vs. 0.44, $p=0.0002$) resulting in a 28% relative risk reduction.

- For the full study duration (mean follow-up 15 months), the rate of HF hospitalizations for the treatment group was significantly lower than the rate for the control group (0.46 vs. 0.73, $p<0.0001$) demonstrating continued efficacy resulting in a 37% relative risk reduction. The treatment effect was particularly dramatic after the 6 month time period with a 44.5 % RRR ($p<0.0001$) in favor of the treatment group. The number-needed-to-treat (NNT) to prevent one HF hospitalization was 4 patients over the study duration.

Secondary Endpoints

- At baseline, both treatment and control patients had similar PA mean pressures. At 6 months of follow-up, the treatment group had a significant reduction of pressures from baseline compared to the control group ($p=0.0077$). In addition, at 12 months of follow-up, the treatment group had a significantly greater reduction of pressures from baseline compared to the control group ($p=0.0299$).

- During the 6 month follow-up period the proportion of subjects hospitalized for heart failure was significantly lower in the treatment group than in the control group

(p=0.0292). The treatment group experienced a greater proportion of patients having freedom from hospitalization than the control group, over the entire follow-up period (p = 0.0242).

- At 6 months, treatment patients had more days alive outside of the hospital (174.4 vs. 172.1, p=0.0280) and fewer days in the hospital (2.2 vs. 3.8, p=0.0246) compared to control patients. The treatment group's advantage continued over full study duration with more days alive outside of hospital (455.4 vs. 443.3, p=0.0417) and fewer days in the hospital (4.3 vs. 6.7, p=0.0188); thus the treatment group had 12 more days alive outside of the hospital. The benefit to the treatment group for days alive outside the hospital increased over the course of the study from 2.3 days at 6 months to 12 days at 15 months mean follow up.

- Treatment patients reported better QOL as assessed by the MLHFQ. At 6 months, the average total score in the treatment group was 45.2 ± 26.4 as compared to the average total score in the control group of 50.6 ± 24.8 (p=0.0236).

- The total MLHFQ score change from baseline to 6 months was also evaluated. The treatment group had a greater improvement in QOL than the control group (-10.6 vs. -7.4) (p=0.0373).

<u>All Cause Hospitalizations</u>

- All cause hospitalizations were non-significantly lower in the treatment group at 6 months (232 vs. 263, p=0.4065) and full study duration (496 vs. 597, p=0.3320) with the difference being driven by the reduction in HF hospitalizations. Importantly, the reduction in HF hospitalizations was not offset by an increase in non-HF hospitalizations in the treatment group: non-HF hospitalizations were virtually identical in the treatment and control groups at 6 months (148 vs.143) and full study duration (338 vs. 343).

<u>Survival</u>

- There was a trend for improved survival in the treatment group at 6 months (HR 0.77, 95% CI 0.40 – 1.51, p=0.4484) and over study duration (HR 0.90, 95% CI 0.61 – 1.34, p=0.6203). The treatment group had significantly better survival without HF hospitalizations at 6 months (HR 0.68, 95% CI 0.49 – 0.94; p=0.0181) and over the full study duration (HR 0.73, 95% CI 0.57 – 0.94, p=0.0146).

<u>Serious Adverse Events</u>

- Over the first 6 months, there were 339 serious adverse events in 121(44.8%) patients in the treatment group vs. 385 serious adverse events in 155 (55.4%) patients in the control

group. SAEs were hospitalizations or deaths. After 6 months, there were 353 Serious Adverse Events (SAE) in the treatment group, compared to 434 events in the control group. Over the entire study duration, the cumulative totals were 692 SAE in the treatment arm and 819 SAE in the control arm. The lower SAE event rate in the treatment arm was predominantly due to the reduced number of HF hospitalizations.

- There was one report of an Unanticipated Serious Adverse Device Event (UADE) involving a "tingling sensation" in a control patient which was adjudicated by the CEC as not device/system related. There were two reports of Serious Adverse Device Events (SADE), due to hemoptysis and a blood clot, both of which resolved without permanent sequelae. The CEC adjudicated both events as device/system related. There were no reports of Unanticipated Serious Adverse Device Events (UADE) or Serious Adverse Device Events (SADE) after the 6 month period.

- The overall risk of major bleeding within 30 days of implant was 0.9% (5/550). For patients on warfarin therapy there was a 1.4% risk of major bleeding (3/213). For patients on ASA/clopidogrel there was a 0.6% risk of major bleeding (2/319). This suggests that the risk of bleeding in this trial was similar to reported event rates for warfarin or clopidogrel.

<u>Complications of Heart Failure Therapy</u>

- The primary safety and efficacy endpoints were analyzed with the inclusion of the 8 treatment group CHFTs due to hemodynamic monitoring. The primary safety endpoints of freedom from DSRC ($p<0.0001$) remained significant. In addition, the primary efficacy endpoint of HF hospitalizations remained significant (20.8% RRR, $p=0.0041$).

- Over the study duration, the primary safety and efficacy endpoints were analyzed with the inclusion of the 18 treatment group CHFTs due to hemodynamic monitoring. The primary safety endpoints of freedom from DSRC ($p<0.0001$) remained significant. In addition, the primary efficacy endpoint of HF hospitalizations remained significant (29.6% RRR, $p<0.0001$).

<u>Creatinine (mg/dL) and GFR (mL/min/1.73m²) at Screening and 6 Months</u>

- There were no significant differences in mean creatinine levels between treatment and control at baseline (1.40 vs. 1.35), 6 months (1.49 vs. 1.41), or at 12 months (1.59 vs. 1.60). In addition, there were no significant changes from baseline to 6 months ($p=0.2829$) or 12 months ($p=0.4812$).

- There were no significant differences in mean GFR between treatment and control at

baseline (60.4 vs. 61.8), 6 months (57.3 vs. 61.7), or at 12 months (53.8 vs. 61.7). In addition, there were no significant changes from baseline to 6 months (p=0.2039) or 12 months (p=0.4479).

- Significantly more control patients underwent dialysis than treatment patients (23 vs. 11, p=0.040). None of the cases of chronic dialysis were due to CHFT and only 2 of the cases of temporary dialysis were due to a CHFT (1 treatment, 1 control). Dialysis was associated with significant mortality, particularly in the control group (15 deaths control, 5 deaths treatment).

Sensor Performance

- Based on CardioMEMS database monitoring, the estimated rate of freedom from recalibration was 96.7%, with a 95% lower confidence of 94.9%. Comparative data (sensor vs. Swan-Ganz) over an average of 265.0 ±168.5 days after implant demonstrated good concordance between the sensor and Swan-Ganz PA mean measurements.

Medical Management

- Guidelines for managing heart failure using pulmonary artery pressures were provided to the investigators. Medication changes occurred more frequently for the treatment group than for the control group (p<0.0001) at 6 months. The more frequent medication changes in the treatment group appear to have been driven entirely by the hemodynamic data since the frequency of non-pressure based medication changes was identical between the treatment and control groups.

- Significant increases in the doses of medications (ACE/ARB, beta blockers, nitrates) were evident for the treatment group compared to the control group at 6 months (p=0.0042, p=0.0481, p=0.0422 respectively). Diuretics were the most frequently changed drug but the diuretic dose at 6 months in the treatment group was not significantly higher than in the control group.

Ejection Fraction

- Benefit was seen in patients with either preserved or reduced EF. Treatment patients with reduced EF (<40%) had lower rates of HF hospitalizations than control patients at both 6 months (0.36 vs. 0.47, p=0.0085) and full study duration (0.50 vs. 0.75, p=0.0001). Similarly, treatment patients with preserved EF (≥40%) had lower rates of HF hospitalizations than control patients at both 6 months (0.18 vs. 0.33, p<0.0001) and full study duration (0.31 vs. 0.65, p=0.0004).

Conclusion

The Champion HF Monitoring System is effective in reducing the occurrence of HF hospitalizations in NYHA Class III heart failure patients. The device is safe with very few device and system related complications occurring over the course of the clinical trial. All primary and secondary study endpoints were successfully achieved. In addition, the safety and effectiveness of the device was maintained during the extended blinded follow up period.

The protocol provided guidelines for medical management to optimize baseline and changes in pulmonary artery pressures. The treatment arm in the CHAMPION trial was compared to a very well-managed control group, as evidenced by their low HF hospitalization rate. The CHAMPION trial results provide compelling evidence that physicians, with knowledge of class III heart failure patients' pulmonary artery pressures, can optimize medical management leading to improved clinical outcomes.

11. **Panel Recommendations**

TBD

12. **FDA Decision**

TBD

13. **Approval Specifications**

TBD