CardioMEMS™ HF System

PA Sensor and Delivery System
Model CM2000

User's Manual

- Do not attempt to use the device before also reading and fully understanding the System Guide.

- Carefully inspect all product packaging for damage or defects prior to use. Do not use product if you see any indication of damage or breach of the sterile barrier.

- This device is supplied sterile for single use only. After use, dispose of the Delivery System. Do not resterilize.

- Caution: Federal (U.S.) law restricts this device to sale by or on the order of a physician.

Contents

Description

The CardioMEMS HF System provides pulmonary artery (PA) hemodynamic data used for the monitoring and management of heart failure (HF) patients. The system measures changes in PA pressure which physicians use to initiate or modify heart failure treatment. The system includes the following components:

- Implantable wireless sensor with delivery catheter
- Patient or hospital electronics system
- Patient database

The wireless sensor is designed for permanent implantation into the distal pulmonary artery. Once implanted, the CardioMEMS PA Sensor provides non-invasive hemodynamic data that is collected in the physician's office, clinic, hospital, or patient's home. The data provided by the system includes:

- PA pressure waveform
- Systolic, Diastolic, and Mean PA pressure
- Heart Rate

This hemodynamic data is transmitted to a secure website that serves as the patient database so that PA monitoring information is available at all times through the internet. Changes in PA pressure can be used in conjunction with heart failure signs and symptoms to guide adjustments to medications.

For information on the operation of the CardioMEMS HF System, please refer to the System Guide. For information on operation of the patient database, please refer to the CardioMEMS HF Website Patient Data Management Guide. For clinical study information, please refer to page 13 of this guide.

Figure 1. PA Sensor

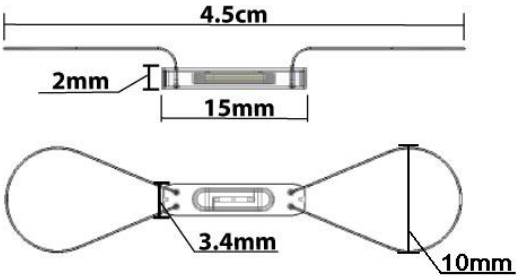


Figure 2. PA sensor and delivery system

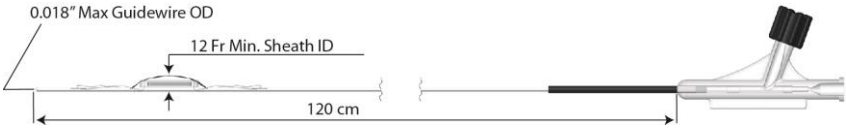


Table 1. Device model numbers

Device	Model number
PA Sensor and Delivery System	CM2000
Patient Electronics System (landline)	CM1010
Patient Electronics System (GSM)	CM1000
Hospital Electronics System	CM3000

Indications

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

Contraindications

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

Clinical Considerations for Patient Selection

The following patients may not be appropriate for implantation of the CardioMEMS HF System:

- 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 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 known coagulation disorders.
- Patients with a hypersensitivity or allergy to aspirin, and/or clopidogrel.
- Patients who have undergone implantation of a Cardiac Resynchronization Device (CRT) within the past 3 months.
- If the patient's BMI is greater than 35, measure the patient's chest circumference at the axillary level. If the chest circumference is > 165cm, sensor implantation should not occur.

Warnings

Before use of the system, read and understand the instructions for use contained in this manual and in the System Guide.

- Read this manual thoroughly before using the system to avoid potential patient injury or death.
- Only trained personnel should use this product.
- The implant procedure must be performed by personnel with the appropriate clinical skills and infrastructure to support right heart catheterizations and endovascular device placement and deployment over a guidewire.
- The PA Sensor and Delivery System is for single use only. Do not reuse, reprocess, or resterilize. Reuse, reprocessing, or resterilization may compromise the structural integrity of the device and/or lead to device failure which, in turn, may result in patient injury, illness, or death. Reuse, reprocessing, or resterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness, or death of the patient.
- The implant procedure must be performed under fluoroscopic guidance.
- Do not use a guidewire with a preformed J-shaped tip for sensor delivery. The preformed J-shaped tip may pull the sensor proximally during guidewire retraction.
- The patient's PA vessel inner diameter must be $\geq$ 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 between the pulmonary artery catheter and the device.

Precautions

- Only authorized personnel should use this device.
- The delivery system should only be used with a guidewire. Do not aspirate or infuse through the delivery system guidewire lumen during use.
- Follow standard procedure for catheterization of patients receiving anti-coagulation therapy. An INR of <1.5 is recommended prior to RHC (Right Heart Catheterization) and implant if on anticoagulant therapy.
- Protect the sensor from surface contamination once removed from the sterile package. Ensure that either talc-less gloves are used for the implantation procedure or rinse all talc from the gloves with sterile saline prior to handling.
- Accuracy of the CardioMEMS HF System is affected by a change in body temperature (-1mm Hg/Δ°C).
- Accuracy of the CardioMEMS HF System is slightly affected by large changes in elevation between the initial baseline calibration and subsequent measurements. (+2mm Hg / 305 meters elevation change).
- An accurate right heart catheterization is required to set system baseline (mean pressure).
- If a patient has a sensor implanted and another member of the same household is scheduled to have a sensor implanted, contact Technical Support prior to the second patient's implant procedure.
- The mean pressure measurement accuracy of the system may be affected by various factors. Mean pressure measurement error has been observed when the sensor was deployed in a vessel which had an inner diameter of less than 7 mm, and in cases

where there was an acute bend in the vessel of >30 degrees at the location of the sensor. Signs of mean pressure measurement error include the following:
  - Gradual mean pressure changes without a corresponding proportional change in the pulse pressure (systolic-diastolic pressure)
  - Negative mean pressures

  If either feature is observed, temporarily suspend use of the pressure information for management of the patient and contact Technical Support for further assistance. Baseline (mean pressure) recalibration may be necessary to continue use of the system.
- Patients who are currently on chronic anticoagulant therapy should restart treatment after 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 procedure. After one month, the patient should continue aspirin therapy.
- Patients with a reduced ejection fraction should be on stable AHA/ACC guidelines based medical therapy prior to implant.
- The PA Sensor is a permanent implant. The sensor does not have any batteries that require replacement or any components that will wear or fail over time. Removal after implantation is not recommended. No circumstances where the sensor needs to be removed have been identified and no sensor has been removed during the clinical trial of the device. The sensor should be retrieved by using standard intra-vascular and surgical procedures as would be used for other vascular implants if required.
- If there is evidence of a change in device performance, contact Technical Support for additional information.
- PA Sensor function is unaffected after temporary exposure up to 2 Atmospheres Absolute (ATA) pressure. Follow the contact process under Technical Support for additional information if the patient will have hyperbaric chamber exposure or is planning to scuba dive.
- Pacemakers, ICD's, and Ventricular Assist Devices (VAD) can work in conjunction with the PA Sensor and will not affect the performance of the system. Several medical procedures can also be performed while the sensor is implanted if precaution is taken to avoid direct contact with the sensor. These procedures include radiofrequency ablation, ionizing radiation, and diagnostic ultrasound. The effects of therapeutic ultrasound have not been determined. If therapeutic ultrasound is required, avoid contact with the sensor.

MRI Information

MR Conditional

Non-clinical testing demonstrated that the sensor is MR Conditional. A patient with this device can be scanned safely, immediately after implantation under the following conditions:

- Static magnetic field of 1.5 or 3.0 Tesla
- Maximum spatial gradient magnetic field of 720-Gauss/cm (7200-mT/m) or less

In non-clinical testing, the CardioMEMS PA Sensor produced the temperatures in the table below during MRI performed for 15 minutes of scanning (per pulse sequence) in the 1.5-Tesla/64-MHz [1] and 3-Telsa/128-MHz [2] MR systems. These temperature changes will not pose a hazard to the patient under the conditions indicated.

Table 2. MRI Related Heating

	1.5-Tesla	3-Tesla
MR system reported whole body averaged SAR	2.9-W/kg	2.9-W/kg
Calorimetry measured values, whole body averaged SAR	2.1-W/kg	2.7-W/kg
Highest temperature change	1.9°C	2.3°C

MR image quality may be compromised if the area of interest is in the same area or relatively close to the position of the sensor. Selecting optimal MR imaging parameters to compensate for the presence of the sensor may be necessary.
The maximum artifact size (as seen on the gradient echo pulse sequence) extends approximately 5 mm relative to the size and shape of the sensor.

Table 3. Artifact Information

Pulse sequence	T1-SE	T1-SE	GRE	GRE
Signal void size	305-mm^2	34-mm^2	645-mm^2	101-mm^2
Plane orientation	Parallel	Perpendicular	Parallel	Perpendicular

Explant and Disposal

The sensor does not require removal before cremation. Do not implant an explanted sensor in another patient as sterility, functionality, and reliability cannot be ensured.

[1] Magnetom, Siemens Medical Solutions, Malvern, PA. Software Numaris/4, Version Syngo MR 2002B DHHS Active-shielded, horizontal field scanner
[2] Excite, HDx, Software 14X.M5, General Electric Healthcare, Milwaukee, WI

Potential Adverse Events

Potential adverse events associated with the implantation procedure include, but are not limited to the following:

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

Instructions for Use

Personnel Training

Implanting physicians are required to have successfully completed additional training in the use of the PA Sensor and Delivery System prior to implant.

Accessories

The accessories required to implant the device and set the sensor's PA pressure baseline are listed in the following table. These accessories are not packaged with the device.

Table 4. Accessories

Item	Specifications
Vascular Access Kit	12 Fr Introducer sheath and dilators with access guidewire
PA Catheter	110 cm length
Sensor Delivery Guidewire	0.018" x 260-300 cm fixed core guidewire with straight or angled tip (no J-tip)

In addition to the specified accessories, the following catheter lab equipment and supplies are required to implant and set the sensor's PA pressure baseline:

- Fluoroscope with digital angiography capabilities and ability to record and recall images (C-arm or fixed)
- Blood pressure monitoring equipment for a right heart catheterization procedure
- Saline solution
- Radiopaque contrast media

Package Inspection

Inspect the package carefully before opening and check the Use By date on the product label. Implant of the sensor is not recommended after its expiration date. If the integrity of the sterile package has been compromised, or the product or package is defective, do not use the product and contact Technical Support.

Package Contents

The sensor is packaged separately and supplied sterile. Packages contain:

- 1 PA Sensor and Delivery System
- 1 USB flash drive
- 1 temporary patient implant card
- Product documentation

Sterilization

The package contents have been sterilized with ethylene oxide before shipment. The system is for single use and is not intended to be resterilized. If the sterile package has been compromised, contact Technical Support.

Pre and Post Procedure Antiplatelet Regimen

Patients who are currently on anticoagulant therapy, or those in which chronic anticoagulant therapy is indicated for heart failure treatment, will restart treatment after sensor implantation. An INR of <1.5 is recommended prior to sensor implant for patients who were previously on anticoagulant therapy. Patients should discontinue use of anticoagulant therapy 1-2 days prior to sensor placement. The standard of care as bridge therapy to sensor placement should be used in patients who were on anticoagulant therapy.

Patients who are not 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 sensor placement. After one month, the patient should continue with aspirin therapy only. It is important to resume or initiate antiplatelet or anticoagulant therapy following sensor implantation to reduce the likelihood of thrombotic events.

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

Implantation Procedure

Hospital Electronics System Setup

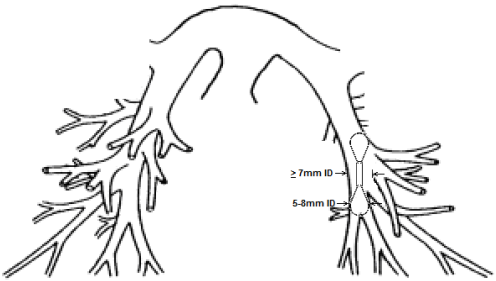
To set up the Hospital Electronics System:

1. Mount the external system on an IV pole.
2. Position the IV pole near the head of the patient and on the same side as the implant site.
3. Plug the power cord into a wall outlet.
4. Insert the USB flash drive that came with the PA Sensor and Deliver System.
5. Turn on the power to the system.
6. Select New Implant.
7. Either select or enter the patient information.
8. Confirm that the sensor serial number displayed on the screen matches the number on the sensor product.
9. Place the right and left ECG electrodes high on the shoulders, and place the reference electrode below the chest. The leads should be routed away from the chest. ECG leads draped near the antenna or antenna cable can reduce sensor signal strength.

Right Heart Catheterization and Sensor Implant Procedure

1. Gain percutaneous access to the left or right femoral vein.
2. Introduce 12Fr introducer sheath over a 0.035mm guidewire.
3. Remove the dilator and guidewire.
4. Insert and advance the pulmonary artery (PA) catheter, with balloon inflated, until it reaches a wedge position in the lower lobe region of the left or right pulmonary artery.
5. Measure PA and PA wedge pressure.
6. Measure cardiac output (optional).
7. Identify target implant site by angiogram through the PA catheter distal lumen (5cc hand injection of radiographic contrast) with the balloon inflated. Care should be taken to verify balloon location and lack of over-wedging prior to contrast injection. Target implant site criteria:
   - Target implant vessel is within the lower lobe of either lung and the vessel is directed towards the feet and back.
   - Vessel diameter is $\geq$ 7 mm and has < 30 degree angulation where body of Sensor will be placed.
   - Vessel diameter is 5 - 8 mm where the distal loop of Sensor will be placed.
   - See figure 3.

Figure 3. Target implant site



8. Insert the sensor delivery guidewire through the PA catheter, across the target implant site.
9. Retract and remove the PA catheter while maintaining the guidewire position.
10. Remove the sensor from the package and flush the guidewire lumen with saline.
11. Carefully swirl the distal end of the catheter (at least 20 cm from the tip) in a bowl of saline to activate the hydrophilic coating.
12. Introduce the sensor delivery catheter over the guidewire through the sheath and into the deployment position at the target implant site.
13. Release the sensor: Unscrew the cap on the delivery catheter hub, then retract and remove the wires from the catheter.

14. Under fluoroscopic monitoring, slowly retract and remove the delivery catheter while maintaining guidewire and sensor position.
15. Insert the PA catheter over the guidewire into the main PA.
16. Slowly remove the guidewire while maintaining sensor position.
17. Position the PA catheter tip approximately 5-10 cm proximal to the sensor or within the opposite lung and measure PA pressure.
18. Acquire the sensor signal using the Hospital Electronics System antenna placed under the patient's back, centered under the sensor position.
19. Set Mean PA Pressure Baseline: Once a valid PA pressure waveform is observed on both the PA catheter and Hospital Electronics System displays, press the "Set Pressure Baseline" button on the Hospital Electronics System. Enter the mean PA pressure value measured by the PA catheter.
20. Set Cardiac Output Baseline: Press the "Set CO Baseline" button on the Hospital Electronics System. Enter the Cardiac Output value which was measured by the PA catheter. (Optional)
21. Press the "Take Reading" button to capture baseline reading(s).
22. Remove antenna from under patient's back.
23. Remove pulmonary artery catheter and introducer sheath.
24. Close venous access site per standard of care.

Patient Identification Card

A temporary patient identification card is provided in the device packaging and should be given to the patient after implantation. Advise patients to keep this card in their possession at all times. A permanent card will be mailed to the patient within a few weeks after discharge.

Patient Counseling Information

Discuss these topics with patients prior to discharge:

- Signs and symptoms of infection
- Reporting symptoms
- EMI and RF Interference

Clinical Study Information

Introduction

Heart failure (HF) is a major public health problem in the United States affecting over 5 million people with over 1 million HF hospitalizations per year. Elevated pulmonary artery (PA) pressures may occur prior to signs and symptoms of HF decompensation and can provide a sound physiologic basis for HF patient management.

The CardioMEMS HF System provides a novel method for measuring PA pressure using a wireless pressure sensor implanted into the PA, an external communication device, and a patient database. The CardioMEMS HF System provides physicians knowledge of PA pressure while the patient is at home allowing them to manage patients proactively with the goal of reducing heart failure hospitalizations.

CHAMPION (CardioMEMS HF Sensor Allows Monitoring of Pressures to Improve Outcomes in NYHA Functional Class III Heart Failure Patients) was a prospective, multicenter, single-blind, randomized, clinical trial in 550 patients across 64 centers in the United States.

Purpose

The goal of CHAMPION was to determine if physicians could reduce HF hospitalizations by managing patient PA pressures using the CardioMEMS HF System.

Methods

Study Design

550 patients with NYHA Class III HF and a prior HF hospitalization within 12 months were randomized to standard of care plus the CardioMEMS HF System (Treatment group; 270 patients) or to standard of care only (Control group; 280 patients). All patients were implanted with the PA Sensor and took daily readings from home. Patients were enrolled regardless of their baseline ejection fraction so that patients with both reduced and preserved systolic function were included. Physicians had access to pulmonary artery pressure information for patients in the Treatment group but not for patients in the Control group.

Following the completion of Randomized Access, patients transitioned to a period of Open Access, during which PA pressures were provided to physicians for patients in both the Treatment and the Control groups. Specifically, physicians continued to have access to the Treatment group's PA pressures in an unchanged manner, whereas access to the Control group's PA pressure was provided for the first time.

Follow-Up Schedule

After right heart catheterization (RHC) and sensor implantation, all patients had follow-up study visits at 1 month, 3 months, 6 months, and every 6 months thereafter until study termination.

Study Endpoints

The primary and secondary endpoints were evaluated after 6 months of patient follow-up. The primary safety endpoints were 1) Freedom from device / system-related complications (DSRC), and 2) Freedom from pressure sensor failures. The primary efficacy endpoint was the rate of HF hospitalizations. All hospitalizations were adjudicated by an independent Clinical Events Committee (CEC) who were blinded to treatment assignment. Secondary endpoints were tested in a hierarchical fashion and included changes in PA pressures, proportion of subjects hospitalized for HF, days alive outside of the hospital for HF, and quality of life. Because blinded follow-up continued until the last patient completed 6 months of follow-up, the average patient follow-up was much longer (17.6 months) and pre-specified supplementary analyses were conducted on the full duration of follow-up data (Randomized Access).

Patient Demographics and Disposition

575 patients were consented for trial enrollment and underwent right heart catheterization. Of these 575 patients, 25 (4.3%) underwent a right heart catheterization but did not receive an implant primarily because of anatomical/physiological conditions identified during the RHC. Of the 550 randomized patients, 270 were assigned to the Treatment group and 280 to the Control group. The two groups were similar with respect to baseline characteristics (Table 5).

Table 5. Patient Demographics

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

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

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

The mean follow-up during Randomized Access was 17.6 months for a total duration of approximately 800 patient years. During the course of Randomized Access, 93 patients in the Treatment group and 110 patients in the Control group exited the study with the primary reason being death.

A total of 347 patients (177 in the Treatment group and 170 in the Control group) completed Randomized Access and entered Open Access. The mean follow-up during Open Access was 13 months for a total duration of approximately 400 patient years. During the course of Open Access, 58 patients in the Treatment group and 43 patients in the Control group exited the study with the primary reason being death.

Primary and Secondary Endpoint Results

Primary Safety Endpoints

CHAMPION met the two primary safety endpoints: (1) Freedom from device/system related complications (DSRC) and (2) Freedom from sensor failure. The protocol pre-specified objective performance criteria (OPC) were that at least 80% of patients were to be free from DSRC and at least 90% were to be free from pressure sensor failure. Of the 575 patients in the safety population, 567 (98.6%) were free from DSRC at 6 months (lower confidence limit 97.3%, $p<0.0001$). This lower limit of 97.3% is greater than the pre-specified OPC of 80% (Table 6a & 6b). There were no sensor explants or repeat implants and all sensors were operational at 6 months for a freedom from sensor failure of 100% (lower confidence limit 99.3%, $p<0.0001$). This lower limit of 99.3% is greater than the pre-specified OPC of 90% (Table 7).

Table 6a. Primary Safety Endpoint – Freedom from Device/System Related Complications

Device/System Related Complications (n=575)		Lower 95.2% Confidence Limit[2]	Objective Performance Criterion (OPC)	p-value[3]
Yes	**No**			
8 (1.4%)[1]	567 (98.6%)	97.3%	80%	p<0.0001

[1] DSRCs (8 total) by group: Consented but not randomized (2), Treatment (3), Control (3)
[2] Exact 95.2% Clopper-Pearson lower confidence limit
[3] p-value from exact test of binomial proportions compared to 80% for all patients

Table 6b. Primary Safety Endpoint – Description of Device/System Related Complications

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

Table 7. Primary Safety Endpoint – Freedom from Pressure Sensor Failures

Pressure Sensor Failures (n=550)		Lower 95.2% Confidence Limit[2]	Objective Performance Criterion (OPC)	p-value[3]
Yes	**No**			
0 (0.0%)	550 (100%)[1]	99.3%	90%	p<0.0001

[1] Pressure sensor failure counts by group: Treatment (0), Control (0)
[2] Exact 95.2% Clopper-Pearson lower confidence limit
[3] p-value from exact test of binomial proportions compared to 90% for all patients

Primary Efficacy Endpoint

The primary efficacy endpoint of the CHAMPION trial was the rate of HF hospitalizations during the first 6 months of Randomized Access. There were 84 HF hospitalizations in the Treatment group compared with 120 HF hospitalizations in the Control group. This difference between the groups represented a 28% reduction in the 6-month rate of HF hospitalization in the Treatment group (0.32 hospitalizations per patient in the Treatment group vs. 0.44 hospitalizations per patient in the Control group, HR 0.72, 95% CI 0.60-0.85, p = 0.0002) (Table 8).

Table 8. Primary Efficacy Endpoint – HF Hospitalization rates During First 6 months of Randomized Access

	Number of HF Hospitalizations	**6 Month HF Hospitalization Rate**	**Hazard Ratio (95% CI) [p-value][1]**
Treatment Group (n=270)	84	0.32	0.72 (0.60-0.85)
Control Group (n=280)	120	0.44	p=0.0002

[1]p-value and hazard ratio from negative binomial regression model

Secondary Endpoints

The four secondary efficacy endpoints were analyzed hierarchically at 6 months (Table 9). At baseline, both Treatment and Control patients had similar PA mean pressures. When compared with patients in the Control group, the patients in the Treatment group had greater reduction in mean PA pressure (p=0.0077); were less likely to be hospitalized for heart failure (p=0.0292); spent more days alive outside of the hospital for heart failure (p=0.0280); and reported a better quality of life (Minnesota Living with Heart Failure Questionnaire) (p=0.0236).

Table 9. Secondary Efficacy Endpoints at 6 Months

	Treatment	**Control**	**p-value**
Change from baseline in mean pulmonary artery pressure, area under the curve (mean mmHg-days)	-155.7 (n=265)	33.1 (n=272)	0.0077[1]
Proportion of patients hospitalized for heart failure (%)	55 (20.4%) (n=270)	80 (28.6%) (n=280)	0.0292[2]
Days alive outside the hospital for heart failure (mean)	174.4 (n=270)	172.1 (n=280)	0.0280[3]

	Treatment	Control	p-value
Minnesota Living with Heart Failure Questionnaire (mean[median])	45.2 [45.0] (n=229)	50.6 [52.0] (n=236)	0.0236[4]

[1] p-value from analysis of covariance with baseline pressure as the covariate
[2] p-value from Fisher's exact test
[3] p-value from Wilcoxon rank sum test after controlling for subject duration in study (i.e., days alive outside the hospital / subject duration x 180)
[4] p-value from two-group t-test

Medical Management

Physicians responded to Treatment patients' elevated PA pressures by making medication changes to lower PA pressures in an attempt to reduce the risk for HF hospitalization. Physicians documented all medication changes for all patients and indicated whether the change was made in response to PA pressures or standard of care information. During the 6-month follow-up period, physicians made 1113 HF medication changes in the Treatment group and 1061 HF medication changes in the Control group in response to standard of care information. In the Treatment group only, physicians made 1404 HF medication changes in response to PA pressures, primarily through diuretics and vasodilators. This incremental HF management in response to PA pressures using the CardioMEMS HF System led to a significant reduction in HF hospitalizations.

Results from the Entire Randomized Access Period

HF Hospitalizations

During the entire Randomized Access period, the rate of HF hospitalizations was 33% lower in the Treatment group than in the Control group (0.46 vs. 0.68 annualized HF hospitalization rates, HR 0.67, 95%CI 0.55-0.80) (Table 10). The magnitude of the effect during the entire Randomized Access period was slightly larger than that seen during the 6-month primary endpoint period (33% vs. 28%), indicating durability of the treatment effect. The number needed to treat (NNT) per year to prevent one HF hospitalization was 4. For every 100 patients treated, 23 HF hospitalizations would be prevented per year.

Table 10. HF Hospitalization Rates During Randomized Access

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

hazard ratio from Andersen-Gill model

Mortality

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

Freedom from Death or First HF Hospitalization

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

All Cause Hospitalizations

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

Death or All Cause Hospitalizations

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

Results from the Open Access Period (Longitudinal Analysis)

In the Open Access period, physicians were given access to PA pressures in the Control group for the first time while access to PA pressures for the Treatment group continued. In the Control group (N=170), new physician access to PA pressures resulted in a 48% reduction in HF hospitalization rates (0.36 vs. 0.68, HR 0.52, 95% CI 0.40-0.69, $p<0.0001^{*}$). In the Treatment group (N=177), continued physician access to PA pressures resulted in the maintenance of low HF hospitalization rates (0.45 vs. 0.48, HR 0.93, 95% CI 0.70-1.22, $p=0.5838^{*}$).

To account for potential longitudinal confounders, the change in HF hospitalization rates in the Control group as result of new access to PA pressures was compared to the change in HF hospitalization rates in the Treatment group. The change in HF hospitalization rates in the Control group was significantly greater than in the Treatment group (HR 0.56, 95% CI 0.38-0.83, p=0.0040[*]), indicating that the significant 48% reduction in HF hospitalization rates observed in the Control group was the result of physician access to PA pressure and not longitudinal effects.

([*]P-values should be interpreted with caution because the analyses including Part 2 data were not specified before the onset of the study and there are various sources of confounding effects which cannot be separated from the treatment effect.)

Treatment Effects in Women

The CHAMPION study was not powered to show statistical significance for gender, thus a complete determination of the effect of the device in women cannot be made. At the request of FDA, a post-hoc gender analysis was conducted for the CHAMPION study, and the initial finding of a treatment-by-gender interaction for the effect of the CardioMEMS device on the HF hospitalization rate was related to (1) fewer women being in the study and the short duration of follow-up leading to a small number of events in women; and (2) the low HF hospitalization rate in Control women due to an early excess of deaths in women in the Control group, which acted as a competing risk to censor the occurrence of hospitalizations for heart failure.

A further analysis of the treatment-by- gender interaction was performed over the full period of Randomized Access and by incorporating death in the Cox Proportional Hazards. When these limitations and confounding issues were evaluated over the full period, there was neither a qualitative nor quantitative treatment-by-gender interaction and the treatment effect remained positive, independent of gender. However, the analyses conducted do not alleviate the possibility of a diminished treatment effect in women. Given the small number of women enrolled and small number of events observed in women, the true treatment effect in this group remains uncertain. In order to further complement and evaluate the results obtained during the CHAMPION study, the effect of the device in women is being studied as part of the post approval study.

The figures below depict the Freedom from HF Hospitalization and Freedom from Death for Men and Women over the Full Randomized Period (Part 1). Figure 6 below depicts the composite endpoint of Freedom from HF Hospitalization or Death for Men and Women over the Full Randomized Period (Part 1). They illustrate the apparent difference in treatment effect by gender. As seen in Figure 4, for HF hospitalizations alone, treatment and control women have similar outcomes. However, as seen in Figure 5, control women had an increased early mortality creating a competing risk for HF hospitalizations i.e., fewer control women were alive to have HF hospitalizations. Figure 6 examines Freedom from HF Hospitalization or Death and indicates a non-significant trend favoring women in the treatment group.

Figure 4. Freedom from HF Hospitalization over the Full Randomized Period (Part 1).

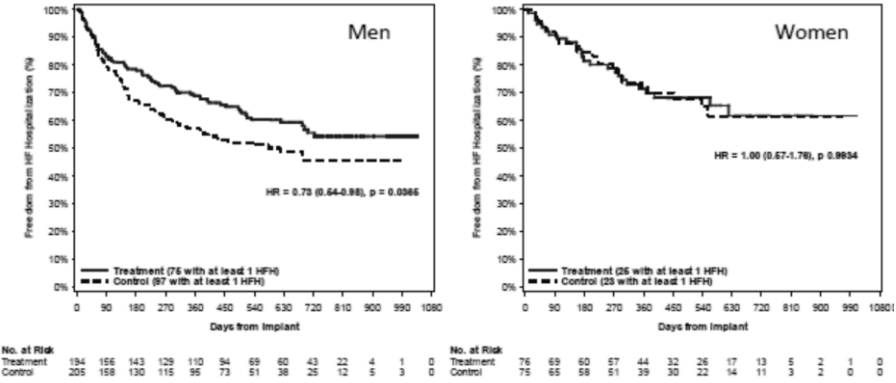


Figure 5. Freedom from Death over the Full Randomized Period (Part 1).

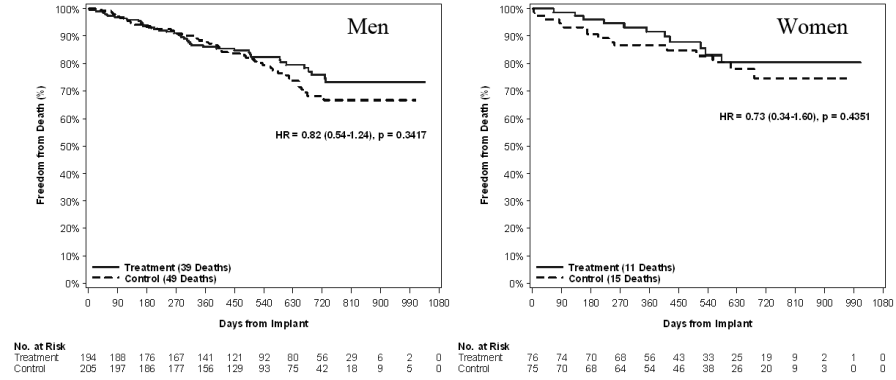
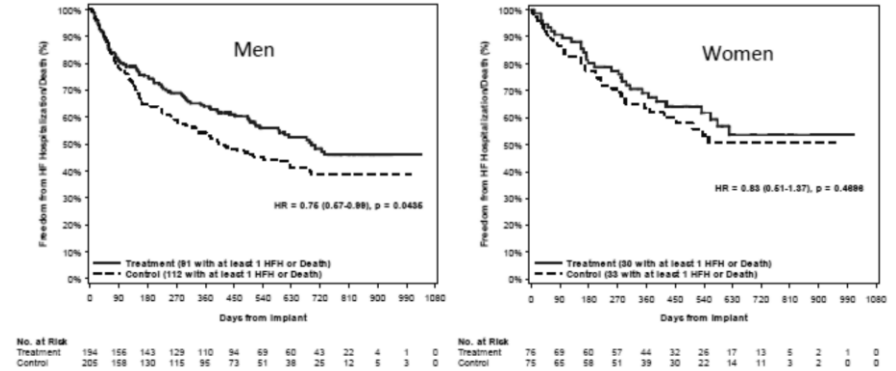


Figure 6. Freedom from HF Hospitalization or Death over the Full Randomized Period (Part 1).



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

Also performed were an Anderson-Gill Model with Frailty, Anderson Gill Model with Robust Sandwich Estimates (RSE) and Negative Binomial Regression using an endpoint of time to HF hospitalization or death in Part 1 and Part 1 + Part 2. As seen in the gray rows in Tables 11 and 12 below, all the competing risk analyses taking death into account as a competing risk show that there was no evidence of a treatment-by-gender interaction if a p-value of 0.05 is used. However, when analyses for interaction by gender are conducted, a p-value of 0.15 is typically used because the analysis is typically not powered appropriately. When considering a p-value of 0.15, there was some evidence of treatment-by-gender interaction in the competing risk analyses under the following models:

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

Table 11. Results of treatment by gender interaction using different statistical models

Models	Estimate	SE	p-value
Part 1			
Cox Model: Endpoint of first HFR hospitalization or Death	-0.113	0.289	0.6968
Cox Model: Endpoint of first HFR hospitalization	-0.330	0.327	0.3131
AG Model with Frailty: Endpoint of HFR hospitalization or Death	-0.373	0.239	0.1211
AG Model with Frailty: Endpoint of HFR hospitalization	-0.531	0.262	0.0459
AG Model with RSE: Endpoint of HFR hospitalization or Death	-0.433	0.316	0.1712
AG Model with RSE: Endpoint of HFR hospitalization	-0.577	0.360	0.1094
NB Regression: Endpoint of HFR hospitalization or Death	-0.412	0.242	0.0896
NB Regression: Endpoint of HFR hospitalization	-0.573	0.191	0.0027
Part 1 + Part 2			
Cox Model: Endpoint of first HFR hospitalization or Death	-0.204	0.249	0.4121*
Cox Model: Endpoint of first HFR hospitalization	-0.427	0.284	0.1331*
AG Model with Frailty: Endpoint of HFR hospitalization or Death	-0.376	0.274	0.1697*
AG Model with Frailty: Endpoint of HFR hospitalization	-0.588	0.271	0.0301*
AG Model with RSE: Endpoint of HFR hospitalization or Death	-0.477	0.274	0.0816*
AG Model with RSE: Endpoint of HFR hospitalization	-0.642	0.313	0.0399*
GEE NB Regression: Endpoint of HFR hospitalization or Death	-0.488	0.283	0.0841*
GEE NB Regression: Endpoint of HFR hospitalization	-0.761	0.319	0.0172*

Table 12. The Treatment vs. Control effects by Gender over Part 1 and over Part 1+ Part 2 under different models

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

(* P-values should be interpreted with caution because the analyses including Part 2 data were not specified before the onset of the study and there are various sources of confounding effects which cannot be separated from the treatment effect.)

Non-Serious Adverse Device Events

There were 17 non-serious adverse device events that occurred over Part 1. There were no additional non-serious adverse device events during the remainder of Part 1 or over Part 2 of the clinical trial. These events were rare and are well known adverse events that occur during right heart catheterization procedures (Table 13).

Table 13. Non-serious Adverse Device Events Over Part 1 and Part 2

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

	Part 1						Part 2	
	TREATMENT (270)		CONTROL (280)		ALL PATIENTS (550)			
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Cardiac disorders	1 (0.4%)	1 (16.7%)	1 (0.4%)	1 (9.1%)	2 (0.4%)	2 (11.8%)	0 (0%)	0 (0%)
Congestive heart failure	1	1	0	0	1	1	0	0
Ventricular tachycardia	0	0	1	1	1	1	0	0
Nervous system disorders	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (9.1%)	1 (0.2%)	1 (5.9%)	0 (0%)	0 (0%)
Dizziness	0	0	1	1	1	1	0	0
Vascular disorders	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (9.1%)	1 (0.2%)	1 (5.9%)	0 (0%)	0 (0%)
Vessel perforation	0	0	1	1	1	1	0	0

Non-Serious Adverse Events not related to the device

Table 14. Non-Serious Adverse Events not related to the device Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
All Patients with an Event	216 (80.0%)	1229	223 (79.6%)	1135	439 (79.8%)	2364	219 (63.1%)	787
Blood and lymphatic system disorders	27 (10.0%)	37	22 (7.9%)	28	49 (8.9%)	65	13 (3.7%)	16
Cardiac disorders	81 (30.0%)	140	69 (24.6%)	117	150 (27.3%)	257	49 (14.1%)	71
Congenital, familial and genetic disorders	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	3 (0.9%)	3
Ear and labyrinth disorders	6 (2.2%)	6	2 (0.7%)	2	8 (1.5%)	8	2 (0.6%)	2
Endocrine disorders	4 (1.5%)	4	9 (3.2%)	10	13 (2.4%)	14	7 (2.0%)	7
Eye disorders	12 (4.4%)	12	14 (5.0%)	16	26 (4.7%)	28	7 (2.0%)	8
Gastrointestinal disorders	64 (23.7%)	104	60 (21.4%)	96	124 (22.5%)	200	48 (13.8%)	70
General disorders and administration site conditions	64 (23.7%)	102	45 (16.1%)	80	109 (19.8%)	182	50 (14.4%)	62
Hepatobiliary disorders	1 (0.4%)	1	7 (2.5%)	10	8 (1.5%)	11	3 (0.9%)	3
Immune system disorders	4 (1.5%)	4	4 (1.4%)	4	8 (1.5%)	8	4 (1.2%)	4
Infections and infestations	76 (28.1%)	129	91 (32.5%)	150	167 (30.4%)	279	65 (18.7%)	99
Injury, poisoning and procedural complications	32 (11.9%)	44	32 (11.4%)	37	64 (11.6%)	81	32 (9.2%)	43
Investigations	32 (11.9%)	51	26 (9.3%)	40	58 (10.5%)	91	22 (6.3%)	25
Metabolism and nutrition disorders	66 (24.4%)	116	52 (18.6%)	88	118 (21.5%)	204	37 (10.7%)	53
Musculoskeletal and connective tissue disorders	49 (18.1%)	75	58 (20.7%)	73	107 (19.5%)	148	56 (16.1%)	70
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (2.2%)	8	9 (3.2%)	9	15 (2.7%)	17	6 (1.7%)	7
Nervous system disorders	61 (22.6%)	86	50 (17.9%)	67	111 (20.2%)	153	47 (13.5%)	56

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Adverse Device Events

Table 16. Unanticipated or Serious Adverse Device Events Over Part 1 and Part 2

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

Unanticipated Serious Adverse Device Events

There was one event during Part 1 reported as a USADE by the investigator but determined not to be serious or device system related by the CEC which reviewed the event on 27 Jun 2009. There were no additional USADEs during the remainder of Part 1 or during Part 2 of the clinical trial.

Serious Adverse Device Events

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

Non-Serious Adverse Device Events

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

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

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

	Part 1						Part 2	
	TREATMENT (270)		CONTROL (280)		ALL PATIENTS (550)			
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Cardiac disorders	1 (0.4%)	1 (16.7%)	1 (0.4%)	1 (9.1%)	2 (0.4%)	2 (11.8%)	0 (0%)	0 (0%)
Congestive heart failure	1	1	0	0	1	1	0	0
Ventricular tachycardia	0	0	1	1	1	1	0	0
Nervous system disorders	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (9.1%)	1 (0.2%)	1 (5.9%)	0 (0%)	0 (0%)
Dizziness	0	0	1	1	1	1	0	0
Vascular disorders	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (9.1%)	1 (0.2%)	1 (5.9%)	0 (0%)	0 (0%)
Vessel perforation	0	0	1	1	1	1	0	0

FCC Statement

This device is approved for wireless transmission under FCC ID number R3PCS-A-000051. This device complies with Part 15 of the FCC Rules. Operation is subject to the following conditions:

- This device may not cause harmful interference.
- This device must accept any interference received, including interference that may cause undesired operation.

Technical Support

For technical support, call 1 877 696 3754.

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