FDA Executive Summary

Prepared for the
October 9, 2013 meeting of the
Circulatory Systems Devices Panel

P100045/A004
CardioMEMS *Champion*™ HF Monitoring System
CardioMEMS, Inc.

Introduction

This is the FDA Executive Summary for the CardioMEMS *Champion*™ HF Monitoring System. The device is an implantable pressure measurement system indicated for measuring pulmonary artery pressures in subjects with New York Heart Association (NYHA) Class III heart failure. Feasibility and Pivotal studies were conducted between October 13, 2006 and March 25, 2010 under IDE G060187. CardioMEMS, Inc. (the Sponsor) submitted a Premarket Approval Application (PMA) for marketing approval of the device (P100045) on December 14, 2010. This submission was reviewed by the Division of Cardiovascular Devices (DCD) within the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA). Results and study conduct issues of the Champion study were presented and discussed by the Circulatory Systems Devices Panel on December 8, 2011. The Panel recommended that there was a reasonable assurance that the device was safe for the proposed indication with a vote of 9 to 1. The Panel voted 7 to 3 that there was not a reasonable assurance that the device was effective for use in the subject population studied due to patient-specific management recommendations contained in nurse communications that confounded the study results. Additionally, the Panel voted 6 to 4 that the benefits of the device do not outweigh the risks in subjects who meet the criteria specified in the proposed indication. After the Panel meeting, FDA issued a Not Approvable (NOAP) letter dated January 11, 2012 for P100045. To address the deficiencies in FDA's letter, the sponsor continued to follow subjects already enrolled in the pivotal study between August 12, 2010, and April 30, 2012. The Sponsor conducted a number of statistical analyses on the additional follow-up data as well as the original data set discussed at the December 8, 2011 Panel meeting. The Sponsor has submitted an Amendment to the PMA that includes the results of these analyses. This PMA Amendment has been reviewed by FDA.

This memorandum will summarize FDA's review of the PMA Amendment highlighting the areas for which we are seeking your expertise and input. These topics will include the additional analyses conducted to address the deficiencies in the NOAP letter. At the conclusion of your review and discussion of the data presented, FDA will ask for your recommendation regarding the benefit risk assessment.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

1 PROPOSED INDICATIONS FOR USE

The CardioMEMS Champion™ HF Monitoring 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 to reduce heart failure hospitalizations.

The CardioMEMS Champion™ HF Monitoring System is used by the physician in the hospital or office setting to obtain and review PA pressure measurements. The CardioMEMS 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.

2 DEVICE DESCRIPTION

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

- Implantable Sensor/Monitor - The Implantable Sensor/Monitor is a battery-free capacitive pressure sensor permanently implanted in the PA.

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

- Champion™ Electronics System and Database - The Electronics System acquires and processes signals from the Implantable Sensor/Monitor and transfers PA pressure measurements to a secure database. The Database receives data transmitted from the Electronics System, and presents the PA pressure data for review by medical professionals, who can make decisions regarding the status of the patient and initiate changes in medical therapy.

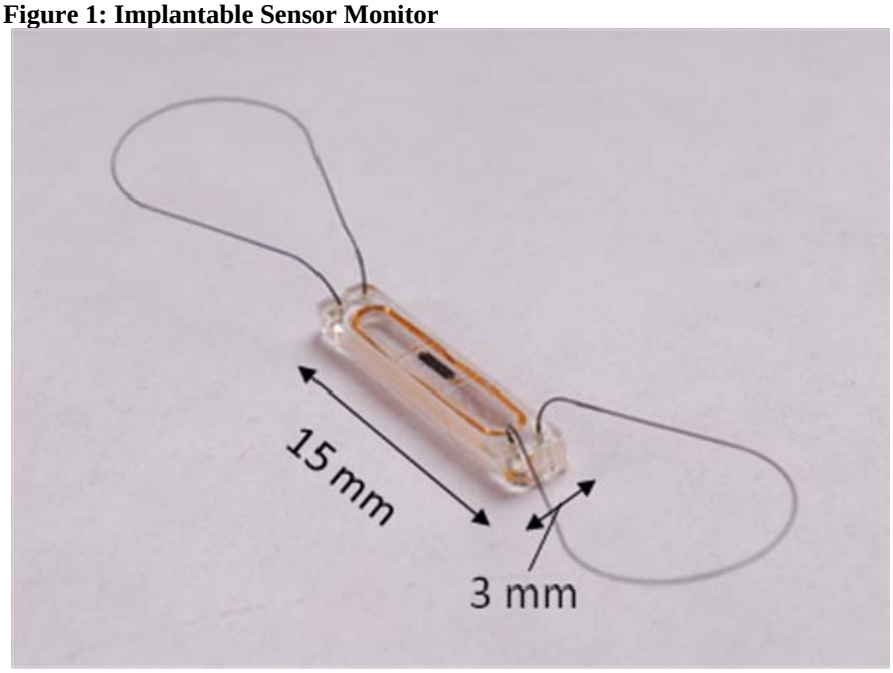
2.1 Implantable Sensor/Monitor

The Implantable Sensor/Monitor consists of a three dimensional coil and pressure sensitive capacitor encased between two wafers of fused silica measuring 15 x 3.41 x 2 mm. The fused silica assembly is completely encased in medical grade silicone. The coil electro-magnetically couples the pressure sensitive capacitor to the Champion™ Electronics System, allowing the remote measurement of the resonant frequency of the circuit without the need for an on-board battery. This resonant frequency is then converted to a pressure measurement.

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

A photograph of the Implantable Sensor/Monitor is provided in Figure 1 below.

Figure 1: Implantable Sensor Monitor



2.2 Delivery System

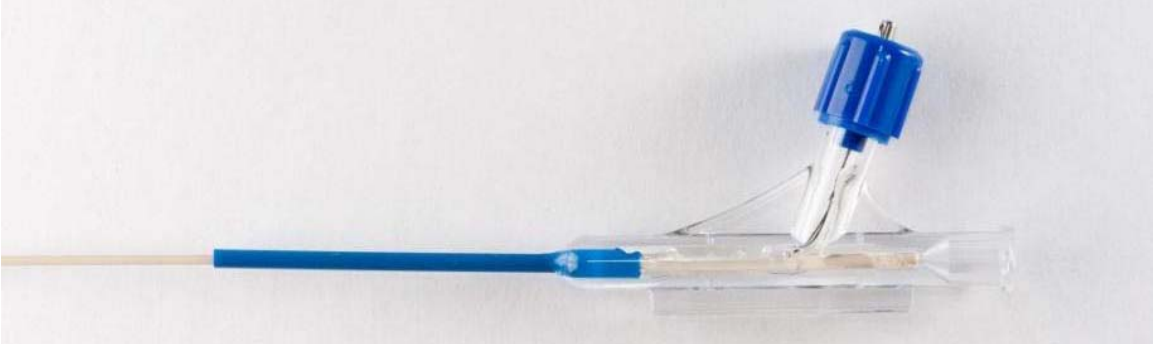
The Delivery System is an over the wire transvenous catheter used to deploy the Implantable Sensor/Monitor. The Implantable Sensor/Monitor is originally attached by tether wires to the Delivery System as shown in Figure 2 below.

The Delivery System includes a hydrophilic coating on the distal portion of the catheter shaft. The Delivery System (with the Implantable Sensor/Monitor) is introduced over a guidewire through an 11Fr sheath. The usable length is 120cm and it is compatible with a 0.018" guidewire.

Figure 2: Distal Section of the Delivery System with Implantable Sensor/Monitor including Tether Wire and Nitinol Loop.

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

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



2.3 *Champion™ Electronics System and Database*

The CardioMEMS Champion™ HF Monitoring System consists of a Champion™ Electronics System and the associated sterile Implantable Sensor/Monitor with Delivery System. The Champion™ Electronics System consists of a Hospital Unit for clinic use and a Home Unit for home patient monitoring. The Hospital and Home Units are identical except for greater functionality in the Hospital Unit including display of the pressure data which is not available on the Home Unit. The Implantable Sensor/Monitor and Champion™ Electronics System are mated to each other with the Champion™ Electronics System preprogrammed for that particular Implantable Sensor/Monitor. The software for the Hospital Unit allows pressure measurements to be visualized on the touch screen during Sensor implant with systolic, diastolic and mean PA pressure as well as a waveform. The software on the Home Unit prompts and guides the patient to make a PA pressure measurement and automatically uploads the information to the Database.

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

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

Antenna

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

Main Unit

The main unit is the location of all the signal generation and processing for the Champion™ Electronics System. The custom circuitry generates bursts of RF energy which powers the Implantable Sensor/Monitor, processes the return signal from the Implantable Sensor/Monitor and transmits pressure information to the single board computer. This circuitry also contains a barometric pressure sensor which provides information to compensate for changes in atmospheric pressure. 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. The Hospital System is illustrated in Figure 4 below.

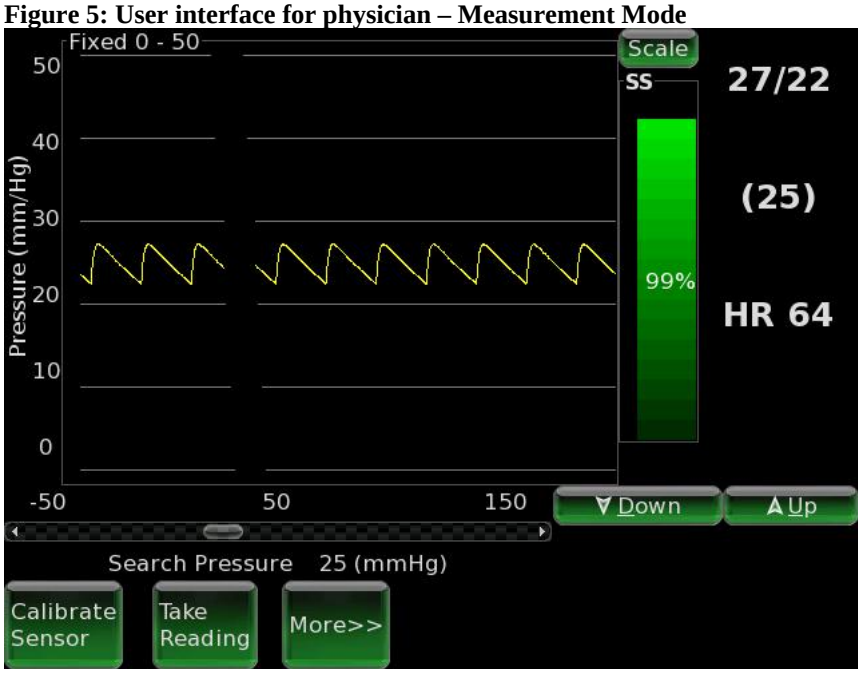
Figure 4: Champion™ Hospital System

Implant Procedure

Once the target vessel has been identified, the Implantable Sensor/Monitor is deployed. A right heart catheter is then placed in the pulmonary artery to obtain pulmonary artery pressure readings for calibration of the Implantable Sensor/Monitor mean pressure values. Using the initial implant mode, the physician is able to collect simultaneous

pressure readings with both the right heart catheter and Sensor. Throughout the procedure, the physician is able to obtain any number of pressure readings.
Figure 5 below is a simulated waveform and data presentation available only for the physician during implant. The patient will see neither a waveform nor a numerical presentation of their pressure reading.

Figure 5: User interface for physician – Measurement Mode



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

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

For additional information on the CardioMEMS Champion™ HF Monitoring System, please see the sponsor's summary.

FDA Commentary 1: The device, including the Champion™ database software, has not been modified. The same version of the device was used throughout the study.

3 Regulatory History and Background Information

The sponsor applied for a feasibility study of the device under Investigational Device Exemption (IDE) application G060187. The first US subject was treated with this system on December 21, 2006 under the feasibility phase of the clinical study (approved on October 13, 2006). The feasibility study was later expanded to twenty (20) subjects

(approved on February 28, 2007). A total of seventeen (17) subjects were enrolled in a non-randomized feasibility study and were implanted with the System. These results were reviewed by FDA, and the sponsor was granted approval to begin enrolling in the randomized, controlled pivotal study on July 18, 2007. The first subject was enrolled in the pivotal study on September 6, 2007.

All subjects enrolled had the device implanted. Subjects randomized to the investigational group were managed by their physicians using the PA pressure data. Subjects randomized to the control group had the device implanted, but data from the device was not made available for making treatment decisions. Following completion of follow-up necessary for analysis of the primary endpoint (referred to as Part 1 or the Randomized Period), PA data was made available for all subjects, including those originally randomized to the control group (referred to as Part 2 or the Open Access Period). The sponsor continued to follow subjects enrolled in the study from the Randomized Period and collect data under the Open Access Period.

The sponsor submitted the PMA for the Champion™ HF Monitoring System on December 14, 2010. Results and study conduct issues of the Champion study were presented and discussed by the Circulatory Systems Devices Panel on December 8, 2011. The panel recommended that there was a reasonable assurance that the device is safe for the proposed indication with a vote of 9 to 1. FDA's review revealed that trial conduct included subject-specific treatment recommendations sent by nurses employed by the sponsor to the treating physicians. These subject-specific recommendations were limited to subjects in the treatment arm of the study. The impact of nurse communications was discussed with the Panel who concluded that the communications severely limited the interpretability of the data in terms of effectiveness. The Panel voted 7 to 3 that there is not a reasonable assurance that the device is effective for use in the subject population studied. The panel voted 6 to 4 that the benefits of the device do not outweigh the risks in subjects who meet the criteria specified in the proposed indication. FDA issued a not approvable (NOAP) letter dated January 11, 2012, which included the following two (2) deficiencies:

1. Please provide FDA with additional data to demonstrate that there is a reasonable assurance of effectiveness of the Champion HF Monitoring System for the proposed Indications for Use. We recommend that CardioMEMS conduct a new, prospective clinical trial to demonstrate the effectiveness of the Champion HF Monitoring System in heart failure management. The new trial should be designed to minimize or eliminate sponsor-driven patient-specific management advice that a) would not be balanced between the investigational and control groups, and b) would not be able to be replicated on a large scale should the investigational device become commercially available. A new trial should also include an assessment of the primary endpoints and mortality through at least 12 months follow-up.

2. The gender analysis showed a statistically significant difference in treatment effect between men and women. Please provide additional data to address potential differences in treatment effect due to gender.

Additionally, FDA requested the sponsor engage an independent external auditor to identify and verify all nurse communications between CardioMEMS and the investigative sites. The results of the audit were sent by the third party auditor to the sponsor and FDA simultaneously. The audit results were reviewed by FDA and were found to be acceptable. Following the audit, FDA requested that the sponsor perform analyses to assess the magnitude of the potential for bias related to the nurse communications. The sponsor provided a Clinical Analysis Plan that included a clinical evaluation of the nurse communications to assess the clinical impact on HFR hospitalizations.

The Sponsor engaged FDA in multiple meetings to discuss the Panel recommendations, FDA deficiencies, and potential resolutions. Instead of starting a new clinical study as requested in deficiency 1 of the Not Approvable letter, the sponsor proposed that the additional follow-up data be analyzed to assess the device's effectiveness in the absence of nurse communications. FDA agreed that this approach might suffice to address the question of device effectiveness and noted that all proposed analyses would be considered ancillary, not primary, analyses. FDA also noted that the analyses would have their limitations, including that the additional follow-up period was not designed with these analyses in mind and that the analyses were not defined prior to the collection of subject data. With these limitations in mind, FDA and the sponsor worked to finalize a statistical analysis plan before any analyses were conducted on the Part 2 (Open Access Period) data.

Figure 6 below is a diagram representing the study timeline for Parts 1 and 2. Each bar represents a single hypothetical study subject and subject events and is not drawn to scale. The mean follow-up is 17 months in Part 1 and 13 months in Part 2. The top group of bars represents 5 hypothetical patients in the Treatment group (Tx), and the bottom groups of bars represent 4 hypothetical patients in the Control group (Cx). The "dotted" filled bars represent those subjects during the timeframe of the 6 month Primary Endpoint. The "lined" filled bars represent those subjects following the endpoint evaluation but prior to the point in time when pressure data was made available regarding control subjects. The "solid" filled bars represent those patients after all subjects' pressure data was available to physicians. Note that following the end of Part 1 of the study, PA pressure data was made available regarding all subjects in the study (identified as green). Part 1 included generic communications to physicians alerting them about a PA pressure change (identified as ✖ in Figure 6) as well as subject-specific treatment recommendations (identified as ★ in Figure 6). This diagram will be used throughout the document to depict the groups being compared in the various analyses. The subject-specific recommendations included recommendations that were consistent with protocol drug change guidelines, as well as some that were inconsistent or not included in the protocol. It is important to note that nurse communications, including generic communications as well as those with subject-specific treatment recommendations ceased prior to the start of Part 2 of the study.

Figure 6: Hypothetical CHAMPION Study Timeline

4 PRE-CLINICAL AND ANIMAL STUDIES

The information related to the Pre-Clinical and Animal Studies has not changed since the last time the device was discussed before the Circulatory System Devices Panel. No new pre-clinical or animal study information was provided to address the previous Panel's recommendation or FDA's Not Approvable letter. No new issues have been identified by FDA related to this material.

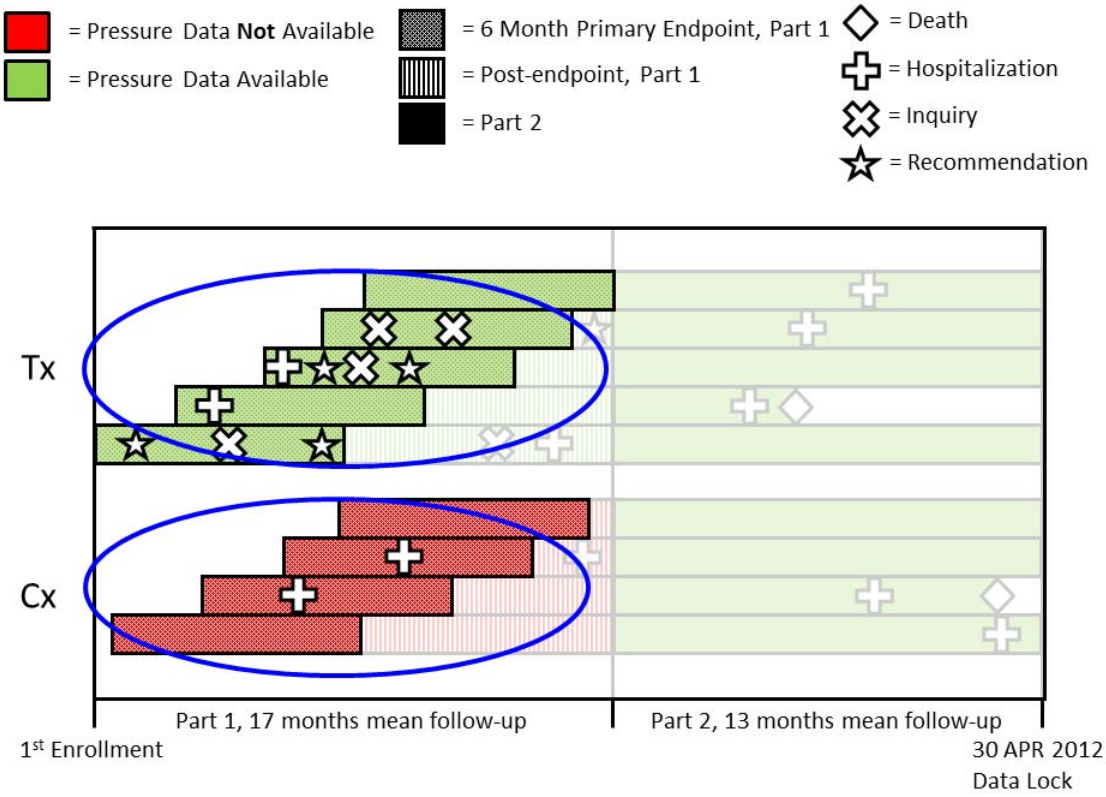
5 CLINCIAL STUDY AND DESIGN

The following discussion of the Clinical Study Design was presented at the December 8, 2011 panel meeting:

The original IDE pivotal trial was a prospective, multi-center, randomized, single-blinded study designed to show the safety and effectiveness of the CardioMEMS HF Pressure Measurement System for the treatment of subjects with New York Heart Association (NYHA) class III heart failure symptoms who have been hospitalized for heart failure in the previous year. The study involved 64 enrolling centers and 550 subjects with a history of symptomatic heart failure (NYHA class III) who had experienced at least one heart failure related (HFR) hospitalization in the year prior to enrollment. There was no restriction in terms of left ventricular ejection fraction (LVEF); however, subjects with

reduced LVEF were required to be on appropriate background medical therapy for heart failure. All subjects received the investigational pressure sensor; after device insertion, subjects were randomized, using a 1:1 allocation ratio, to the treatment arm (physician access to the sensor pressure data to help guide medical management, standard medical therapy for heart failure) or the control arm (no physician access to the sensor pressure data, standard medical therapy for heart failure). An independent clinical endpoints committee (CEC), blinded to the treatment groups, reviewed abstracted clinical data and determined when the criteria for a protocol-defined heart failure hospitalization were met. An independent, blinded Data Safety Monitoring Board (DSMB) reviewed available safety and effectiveness data. This Randomized Access Period was defined as Part 1 of the study and included evaluation of the pre-specified primary endpoints as seen in Figure 7 below.

Figure 7: CHAMPION Trial Pre-specified Study Endpoints



Following the completion of this period of Randomized Access (Part 1), the investigators continued to receive PA pressure data for treatment group subjects, and began to receive PA pressure data for control group subjects. Therefore subjects in Part 1 transitioned to a period of Open Access, defined as the Part 2 of the study. During Part 2, physicians received automated alerts and had access to subject PA pressure measurements regarding all subjects (both treatment and control groups) but received no CardioMEMS nurse subject-specific treatment recommendations. Importantly, an independent third party audit confirmed that no CardioMEMs nurse subject-specific treatment recommendations took place after the end of Part 1 of the study.

Following the December 8, 2011 Panel recommendations and FDA Not Approvable Letter, the sponsor had multiple discussions with FDA that developed a series of detailed Statistical Analysis Plans (SAP) for the proposed ancillary analyses of the Part 2 data. These ancillary analyses were used to evaluate outcomes when all subjects' physicians received access to pulmonary artery (PA) pressure information during Part 2 of the study. Part 2 study results were compared to the original results (Part 1 of the trial). Specifically, the longitudinal analyses, discussed below, focused on the changes in the HFR hospitalizations as the subjects transitioned from Part 1 to Part 2. These analyses also evaluated the impact of introduction of the knowledge of PA pressures to physicians treating subjects in the control group, but at a later point of the trial and un-confounded by nurse communications. Table 1 below outlines the differences between the trial periods, randomized groups, and trial components. FDA provided extensive input to the sponsor's proposed SAP and ultimately agreed with the ancillary analyses to be performed and the parameters to be used in the analyses, while pointing out the inherent limitations of the proposed analyses, discussed below.

Table 1: Distinctions for Part 1 (original trial) and Part 2 of the trial.

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

5.1 Enrollment Criteria

5.1.1 Inclusion Criteria

The Inclusion Criteria did not change from Part 1. New covariate information was not obtained at the onset of Part 2. The key inclusion criteria for Part 1 were:

- NYHA class III heart failure
- At least one HF-related hospitalization with 12 months prior to enrollment.

Other key study inclusion criteria in Part 1 were:

- Body mass index (BMI) must be <35 or, if >35, additional body habitus assessments required (see required pre-implant procedures below)
- PA branch in which sensor will be deployed must be 7-15 mm in diameter.

5.1.2 Exclusion Criteria

The Exclusion Criteria did not change from Part 1. The key study exclusion criterion was:

- More than 1 pulmonary embolus (PE) or deep vein thrombosis (DVT).
  Note: Enrollment was not limited by LVEF.

5.2 Original PMA Statistical Analysis Plan

The following information was discussed and presented at the December 8, 2011 Panel Meeting.

The Original PMA Statistical Plan pre-specified analysis populations for Intent-to-Treat (ITT), Per Protocol (PP), and Safety Population.

The primary effectiveness endpoint compared the rate of HFR hospitalizations through six (6) months in each arm.

There were two primary safety endpoints:

1. Freedom from a device/system-related complication (DSRC) through six (6) months tested against a performance goal.
2. Freedom from pressure sensor failure through 6 months tested against a performance goal.

Additionally, there were four (4) secondary effectiveness endpoints analyzed at the six (6) month visit, which included:

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

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

Supplementary Analyses were also performed and included:

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

5.3 Effectiveness Analyses: Part 1 and Part 2 Statistical Analysis Plan

As stated above, the sponsor and FDA worked interactively through multiple meetings to establish a SAP that would be used to address FDA's Not Approvable letter and previous Panel recommendations. The various analyses conducted under this SAP are described below.

FDA Commentary 2: Although these analyses were designed by the sponsor in consultation with FDA, it is important to note that they are considered ancillary analyses because no study success criteria could be defined a-priori and because the study was not originally designed with these analyses in mind. Although p values are presented along with the results of these ancillary analyses, caution should be used when interpreting the results because the study is not powered for these analyses, multiple analyses were conducted on the same data, and preservation of Type I error was not attempted. The sponsor decided to proceed with these analyses despite their limitations because the sponsor believed that the totality of the additional effectiveness data would be persuasive when interpreted in a reasonable clinical light.

5.3.1 Longitudinal Analyses of HF Hospitalizations over Part 1 and Part 2 using Combined Data of Parts 1 and 2

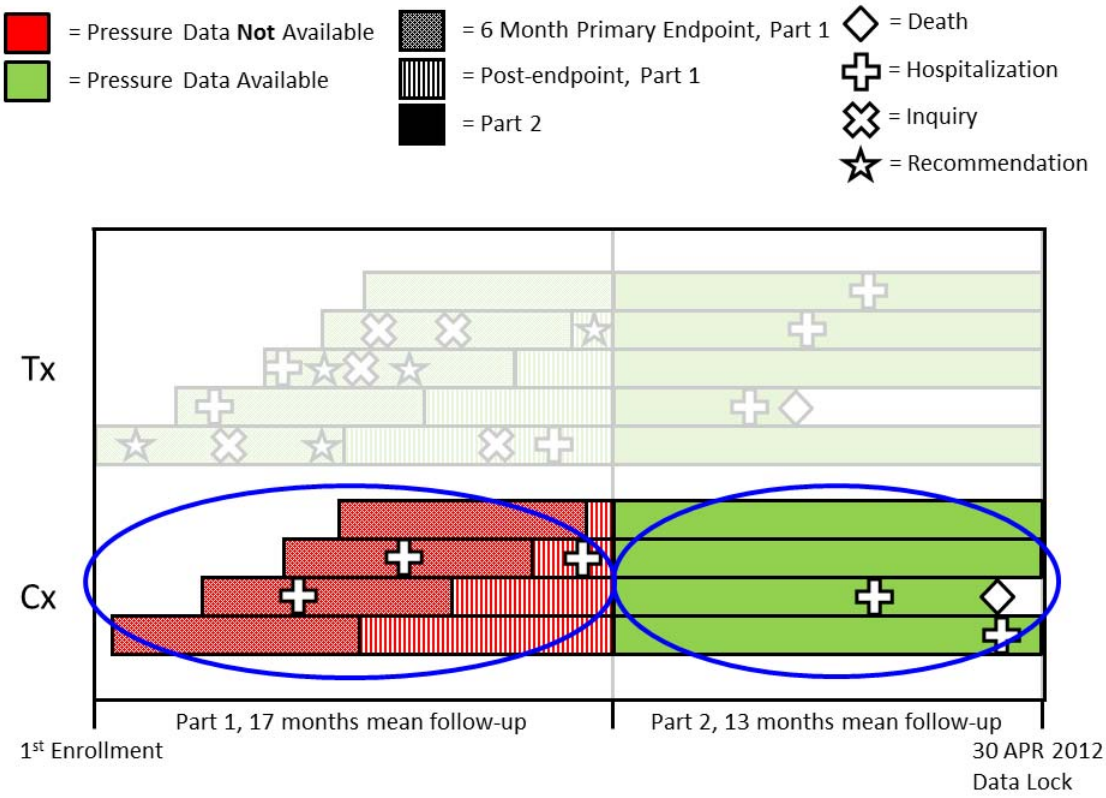
The longitudinal analyses in this PMA amendment were based on the Randomized Access phase (Part 1) and Open Access phase (Part 2). The original PMA focused on the differences in the rate of HFR hospitalization between Treatment and Control groups for Part 1 data. The new longitudinal analyses provided in this PMA amendment compared the rate of HFR hospitalization as the subjects were followed during Part 2. These new longitudinal analyses were designed to further evaluate if knowledge of PA pressures, un-confounded by nurse communications, reduced the rate of HFR hospitalizations.

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

To assess the difference in HFR hospitalization rate among subjects managed with PA pressure data and those without it, the following four comparisons were performed:

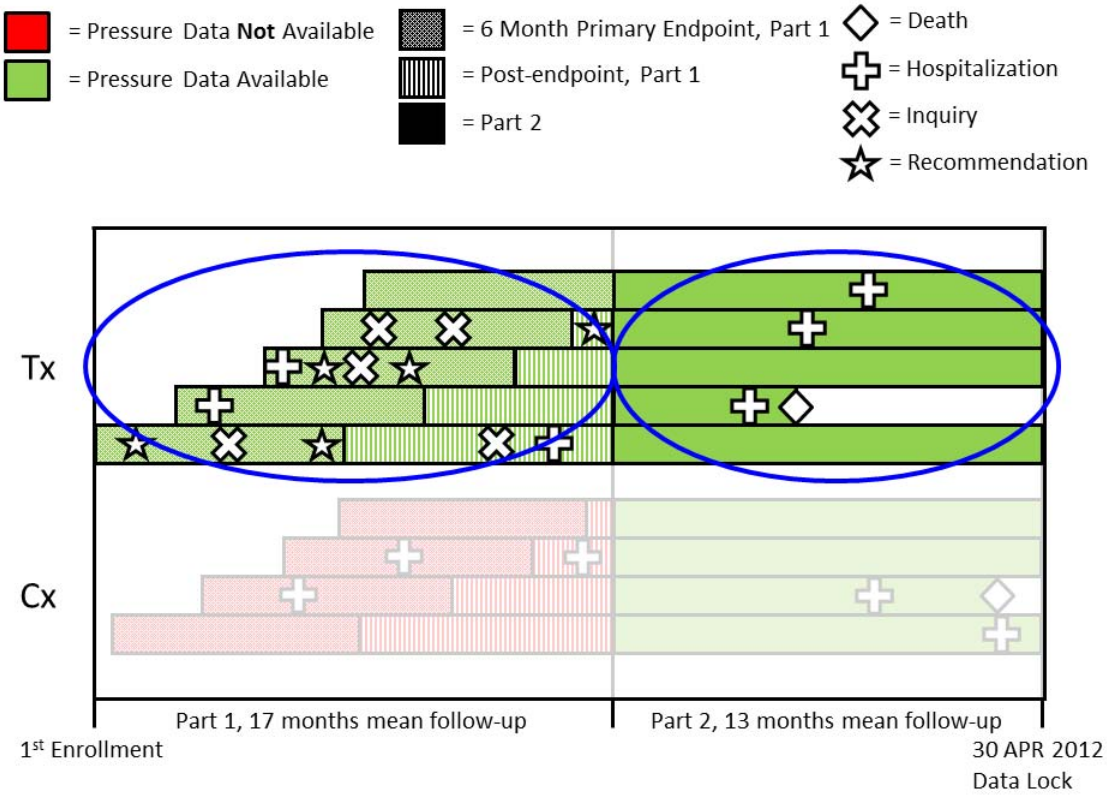
1. Comparison of Former Control (Part 2) to Control (Part 1)
   The analysis was intended to determine whether the HFR hospitalization rate was lower in the Former Control group (Part 2) than the Control Group, where the Former Control group was exposed to treatment (access to PA pressures) without nurse communications. The Control group was not exposed to the treatment. This is illustrated below in Figure 8.

Figure 8: Comparison of Former Control (Part 2) to Control (Part 1).



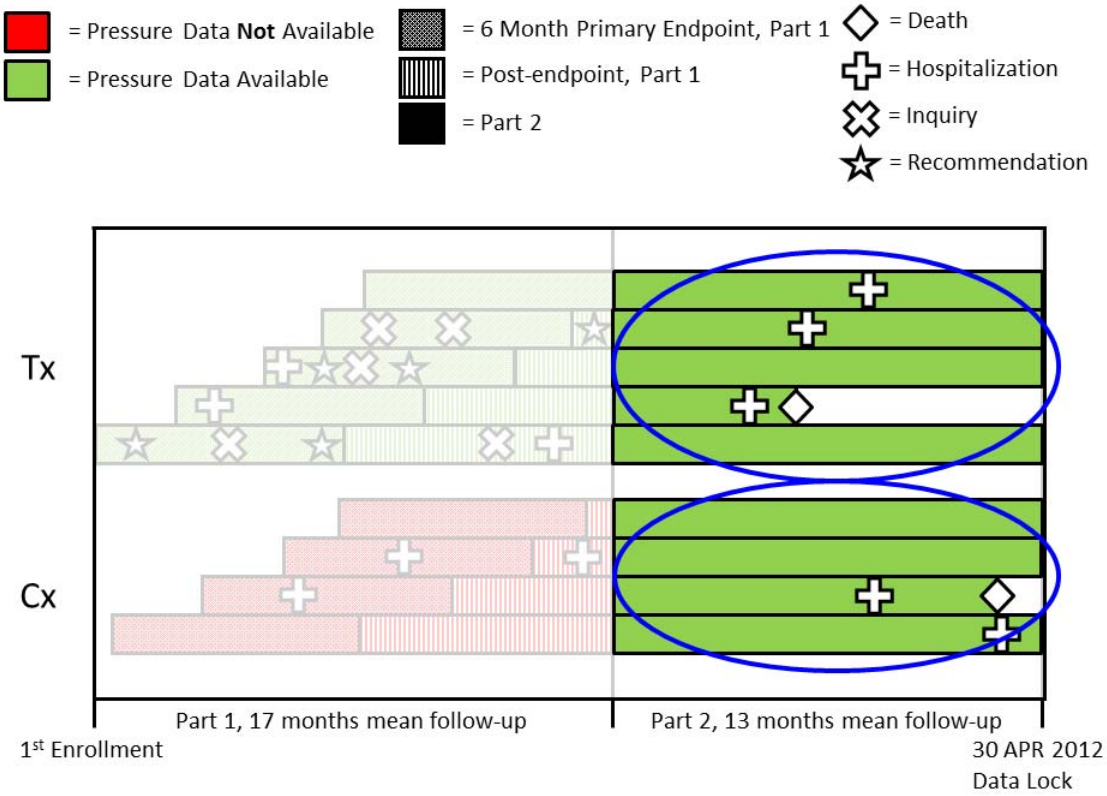
2. Comparison of Former Treatment (Part 2) to Treatment (Part 1)
   The analysis was intended to evaluate whether the HFR hospitalization rates remain the same in subjects whose access to PA pressures remained unchanged, but no longer received nurse communications. This is illustrated below in Figure 9.

Figure 9: Comparison of Former Treatment (Part 2) to Treatment (Part 1).



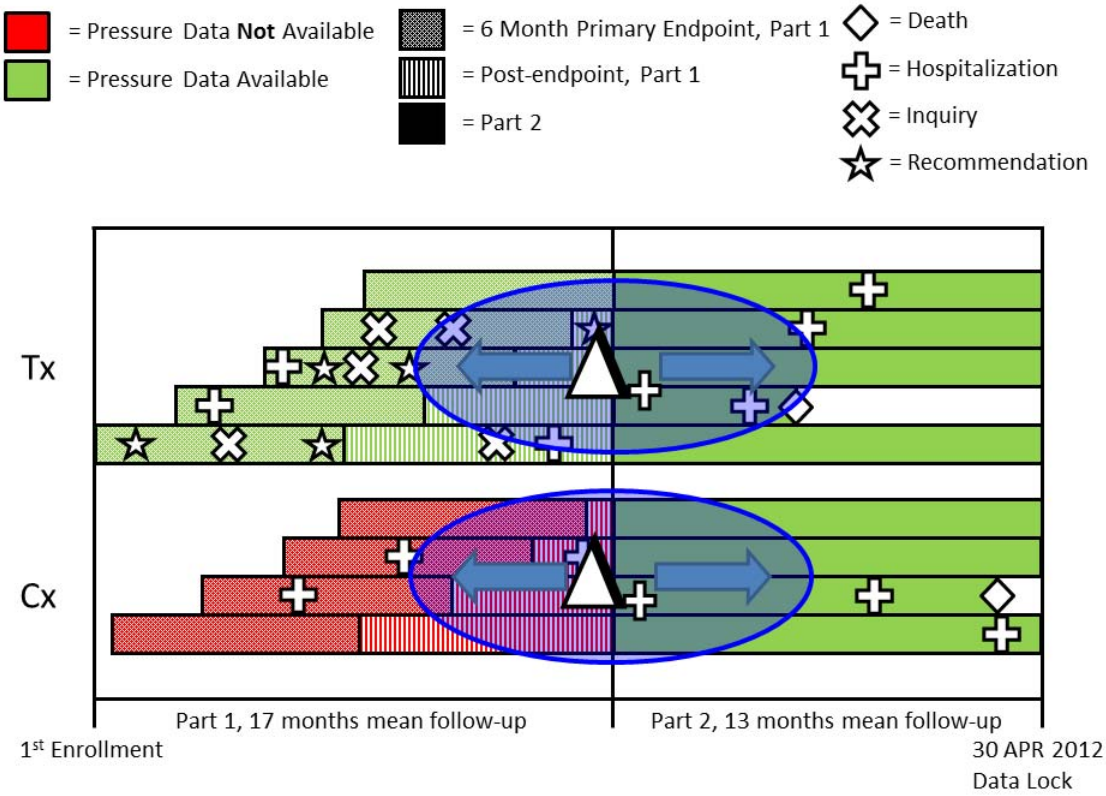
3. Comparisons of Former Control (Part 2) to Former Treatment (Part 2)
   The goal of this analysis was to demonstrate that the rate of HFR hospitalizations was similar during Part 2 when both groups were managed in an identical fashion (access to PA pressure and no nurse communications). This is illustrated below in Figure 10.

Figure 10: Comparisons of Former Control (Part 2) to Former Treatment (Part 2)



4. Change in HF Hospitalization Rates in the Control group (Part 2 vs. Part 1) compared to the Change in HF Hospitalization Rates in the Treatment group (Part 2 vs. Part 1)
   This analysis was intended to demonstrate that the magnitude of change in HFR hospitalization rates after the transition from Control to Former Control (Part 1 vs. Part 2) was greater than the magnitude of change in HFR hospitalization rates after the transition from Treatment to Former Treatment (Part 1 vs. Part 2). This is illustrated below in Figure 11.

Figure 11: Change in HFR Hospitalization Rates in the Control Group vs. the Treatment Group.



A detailed description of the statistical methods used for each of these analyses can be found in Appendix A.

It should be noted that if the model assumptions for these analyses do not hold, then the results of the analyses are not valid. Therefore, it is important to assess the model assumptions and robustness of any conclusions. The sponsor performed multiple supporting analyses to evaluate the assumptions and robustness including:

- Proportional Hazards and Independence of the Recurrent Hospitalization used in the A-G model;
- Robustness of the A-G model;
- Longitudinal analyses using individual data from Part 1 and Part 2;
- Competing risk analysis to assess the impact of death when it is considered an event;

- Covariate adjusted analysis; and
- Analysis to evaluate missing data.

Additional details regarding the supporting analyses can be found in Appendix A.

5.3.2 Clinical analysis of the impact of nurse communications, identified through the third party audit, on the rate of HF hospitalizations on Part 1 data.

The sponsor assessed the impact of the clinical nurse communications with the goal of identifying and discussing the potential influence on the rate of HFR hospitalization. FDA and the sponsor agreed to the approach of utilizing two cardiologists, acting independently of each other, with expertise in HF and clinical trials and who had not been involved in the design, recruitment, execution, or initial analysis of the CHAMPION study, to perform the clinical analyses. A nurse communication was defined as potentially providing a treatment recommendation if the text of the communication referred to the potential desirability of, or the need for, a change in a specific type of medication or treatment, regardless of whether the text referred to a class of drug, a specific agent by name, or a specific does or specific route of administration. The concordance between a treatment recommendation and a medication change was considered 'concordant' if the medication change took place within a specified period, ranging from 0-2 to 0-7 days, of having received the nurse communication. Furthermore, the medication change was labeled as 'consistent' or 'not consistent' with the study protocol. The cardiologists classified the nurse communications as either:

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

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

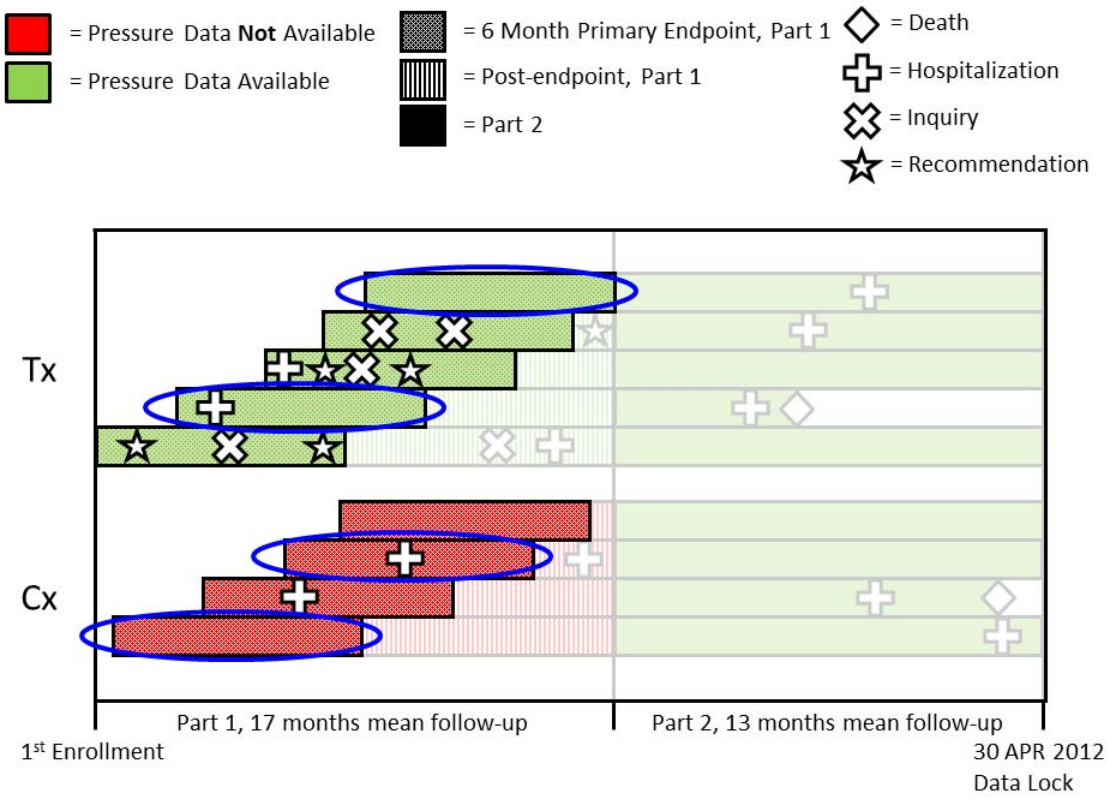
Importantly, this analysis also served as a method to establish the appropriate time point after which the data should not be considered biased by nurse communications.

5.3.3 Propensity Analysis: Quantitative Analysis of Impact of Nurse Communications for Part I data

The sponsor assessed the influence of CardioMEMS nurse communications by performing a Propensity Score model that was developed with FDA input prior to any final data analysis. The Treatment Group (N=270) was divided based on whether the study subjects were the topic of a nurse communication. Those subjects in the Treatment Group who never received a nurse communication were placed in the Treatment No Nurse Communications (TNNC) group (N=99). This is illustrated in Figure 12 below. The propensity modeling, using one-to-one nearest neighbor approach, matched the cohort of TNNC group with a comparable group of subjects in the Control group (N=99). An independent statistician evaluated and included the baseline variables in the final propensity model, using backward elimination, with the threshold for retaining a variable

in the model at p<0.3. A Propensity Model with all covariates forced into the model was also considered. The propensity score was calculated using logistic regression with a treatment indicator as the outcome variable.

Figure 12: Propensity Matched Subjects with no Communications.



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

The final propensity model and the matched data were provided to a separate and independent 3rd party data analysis center for the outcome analysis, i.e. 6 month HFR hospitalization rates (Primary efficacy endpoint in the original PMA).

5.3.4 Gender Analysis

The sponsor carried out an ancillary subgroup analysis of 6 month HFR hospitalization based on gender as an amendment to the original analysis. The original analysis noted a statistically significant treatment by gender interaction. In order to examine whether the treatment-by-gender interaction was driven by early deaths in the control group females, the composite endpoint of "death or first HFR hospitalization" was analyzed using a Cox proportional hazard model over Part 1 and the full duration of Part 1 plus Part 2. The concern was that death had created a significant competing risk problem in Control group women and therefore led to lower HFR hospitalization rates, since early death precludes the possibility of further HFR hospitalizations. In addition, the endpoints of time to first HFR hospitalization over Part 1 and over full Duration Part 1 + Part 2 were assessed in the Cox proportional hazard model.

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

5.3.5 Supplementary Analysis

In addition to the main analyses above, the following additional comparative analyses were conducted:

1. Rate of HFR hospitalization for the full period of Randomized Access inclusive of the final 2.5 months.
2. Proportion of subjects hospitalized over the entire study duration.
3. Mortality over the entire study duration.
4. Effect of the device on Quality of Life.

6 STUDY RESULTS

6.1 Baseline Demographics and Disposition

A total of 550 subjects were implanted with the device and then randomized 1:1 to either the Treatment group (n=270 subjects) or to the Control group (n=280 subjects). A total of 347 subjects (177 in the Treatment group and 170 in the Control group) completed the full period of Randomized Access (Part 1). During the course of Part 1, 93 subjects in the Treatment group and 110 subjects in the Control group exited for reasons described in Figure 13 below. The average duration of follow-up for Part 1 was 533.5 days in the Treatment group and 524.7 days in the Control group. For Part 2, the average duration of follow-up was 372.7 days in the Former Treatment group and 405.4 days in the Former Control group.

Subject demographics and medical history were reasonably matched between the Treatment and Control arms in Part 1 and between the Former Treatment and Former

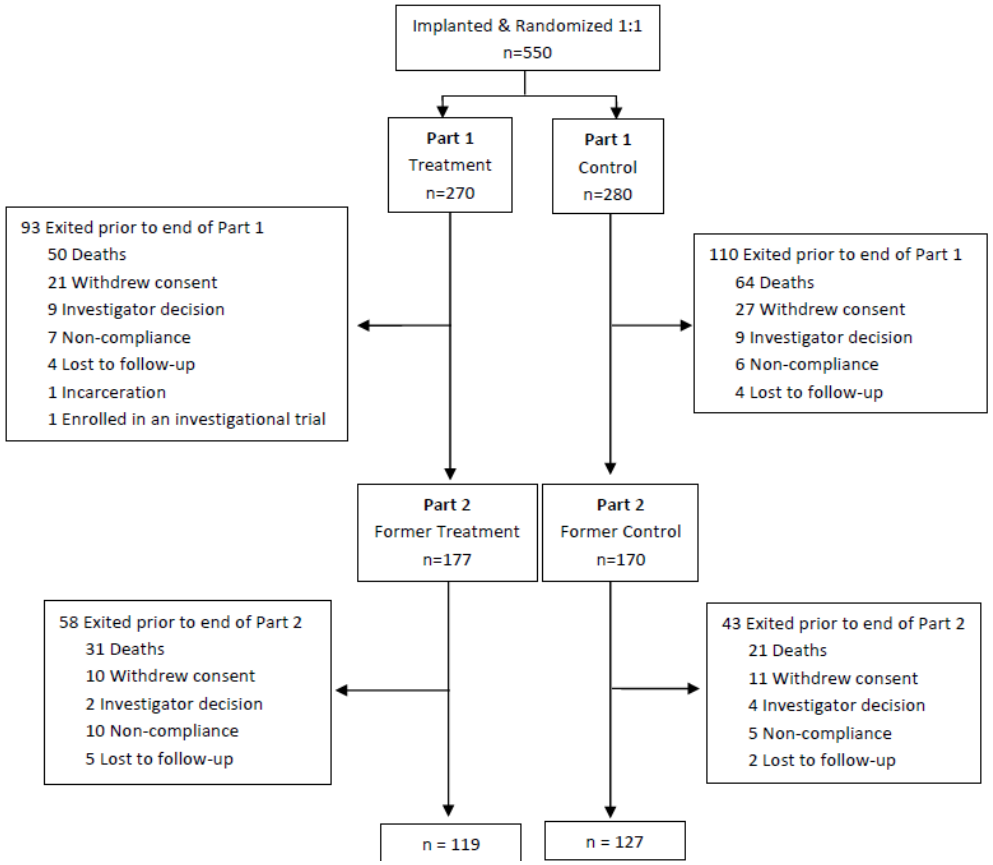
Control in Part 2 in regard to their original baseline characteristics which were measured prior to the onset of Part 1.

The patient demographics for Part 1 and Part 2 are included below in Table 2. The data for Part 2 uses the same measures of covariates as Part 1 for subjects entering Part 2. Measures of covariates for subjects entering Part 2 were not collected at the start of Part 2.

Table 2. Patient Demographics for Part 1 and Part 2.

Demographics	**Part 1**	**Part 2**
Mean Age	61.6 ± 12.8 years old	60.3 ± 12.4 years old
Male	72.6%	63.7%
Caucasian	72.9%	69.7%
Average BMI	30.7 ± 6.9	31.3 ± 7
Average LVEF	29.1% ± 13.6%	29.8% ± 14.4%
LVEF < 40% for randomized	78.3%	76.1%
Ischemic Cardiomyopathy for randomized	60.3%	57.4%
Average PA Systolic (mm Hg)	44.9 ± 14.7	42.8 ± 14.4
Average PA Diastolic (mm Hg)	18.9 ± 8.3	17.9 ± 8.5
PA Mean (mm Hg)	29.4 ± 10	28 ± 10
Average PCWP (mm Hg)	18.2 ± 8.07	17.1 ± 8.3
Average Cardiac Output	4.5 ± 1.5 L/min	4.7 ± 1.4 L/min
Average Cardiac Index	2.2 ± 0.6 L/min/m2	2.2 ± 0.6 L/min/m2

Figure 13: Part 1 and Part 2 Subject Disposition



As seen in Figure 13 above, the non-compliance rate appeared to double comparing the Treatment group in Part 1 to the Former Treatment group in Part 2 (7/270 or 2.6% vs. 10/177 or 5.6%). A similar doubling was not observed in the non-compliance rate in the Control and Former Control groups.

Additionally, FDA has assessed the Deaths that occurred during Part 2 of the study in Table 3 below. There was a relative reduction in the death rate of 29% ((17.5% - 12.4%) / 17.5%) comparing the Former Control group to the Former Treatment group.

Table 3: Number of deaths in Part 1 and Part 2 of the study.

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

FDA Commentary 3: 93 out of 270 (34%) subjects in treatment group did not enter Part 2 of the study. 110 out of 280 (39%) subjects in control group did not enter Part 2 of the study. FDA that bias may be introduced due to the non-random exiting of subjects prior to the onset of Part 2. It appears that the subjects who exited in the Control group were similar to those who exited in the Treatment group with respect to their baseline

characteristics (as measured at the start of Part 1). However, the clinically important covariates were not collected at the beginning of Part 2, which started a mean time of approximately 525 days after the baseline covariates were measured. It is possible that the values of some important covariates changed from Part 1 to Part 2. Using Part 1 baseline values for those covariates in the proposed combined data analysis approach may not be appropriate. Furthermore, because of the lack of the covariates at the baseline of Part 2 study, FDA was not able the evaluate:

1. *if the subjects in Part 1 and Part 2 were comparable after subjects exited from the duration of Part 1;*
2. *if important covariates between the comparison arms remained balanced in Part 2; and*
3. *if subjects in Part 2 study still met the trial inclusion/exclusion criteria.*

The mortality in Treatment groups changed from 18.5% in Part 1 to 17.5% in Part 2. This similarity in mortality is expected since the Former Treatment group continued to have access to PA pressures. The mortality in the Control groups decreased from 22.9% in Part 1 to 12.4% in Part 2. Although a decrease in mortality was expected in the Control groups due to PA data availability in the Former Control group, one would have expected the rate to be similar to that of the Treatment group in Parts 1 and 2, approximately 18%. The fact that the mortality rates in the Former Control group is 12.4% versus 17.5% in the Former Treatment may suggest a difference in the patient populations in Part 2 of the study.

The increase in subject non-compliance (e.g., not taking PA readings, not taking medications, not complying with study visits) in the Treatment group as compared to that in the Control group raises two potential issues:

1. *The difference may suggest a difference in the study group populations.*
2. *In order for the device to be effective in reducing HFR hospitalizations, subject compliance is important. It is unclear whether the observed difference in compliance suggests a trend of increasing non-compliance over time.*

Therefore, the results from all longitudinal analyses described in Section 6.3.1 below should be interpreted with caution as the benefits of randomization may not be realized in Part 2. It is unclear whether there are significant differences in the Former Control and Former Treatment groups in Part 2 of the study.

In Question #1, the Panel will be asked to consider the impact of the unknown patient demographics at the onset of Part 2 of the study on the validity of the ancillary analyses described in Section 5.3 above.

6.2 Original PMA Study Results

The following results were discussed and presented at the December 8, 2011 Panel Meeting. The safety endpoint was determined to be met. The effectiveness endpoint was determined to be confounded by a combination of factors that included patient-specific management recommendations contained in nurse communications that confounded the

study results, the statistical methods used by the sponsor were not robust, and the subgroup gender analysis did not demonstrate a benefit in women. Despite the limitations with the effectiveness endpoint interpretation, these results are included below.

The Primary Safety Endpoint #1 captured freedom from a DSRC through 6 months and was tested against a pre-specified performance goal of 80%. The results of the Primary Safety Endpoint #1 can be seen below in Table 4.

Table 4: Part 1 Primary Safety Endpoint #1.

Acute Safety Results	Sample Size N=575
Number of subjects free from a DSRC	567 (98.6%)
95.2% Lower Confidence Boundary	97.3%
p-value of H_0: Rate $\geq$ 80%	<0.0001

The Primary Safety Endpoint #2 captured freedom from pressure sensor failure rate through 6 months and was tested against a pre-specified performance goal of 90%. There were zero (0) pressure sensor failures out of 550 implanted devices. The freedom from pressure sensor failure rate was 100% with a 95.2% LCB of 99.3%.

The Primary Efficacy Endpoint captured the rate of HFR hospitalizations through 6 months and can be seen in Table 5 below.

Table 5. HFR Hospitalization Rate Through 6 Months

	TREATMENT (270)		CONTROL (280)	
	# Hosp.	Hosp. Rate (events/ patient-6 mo.)	# Hosp.	Hosp. Rate (events/ patient-6 mo.)
Up to 6 Months	84	0.32	120	0.44

There were four Secondary Effectiveness Endpoints for which hypothesis testing was pre-specified and were tested in the order listed in Table 6 below.

Table 6. Secondary Effectiveness Endpoints

	Treatment (n=270)	Control (n=280)
Change from baseline in mean pulmonary artery pressure, area under the curve (mean mmHg-days)	-155.7	33.1
Proportion of patients hospitalized for heart failure (%)	55 (20%)	80 (29%)
Days alive outside the hospital for heart failure (mean)	174.4	172.1
Minnesota Living with Heart Failure Questionnaire (mean)	45.2	50.6

The sponsor also assessed the HFR Hospitalization Rates during the full period of Randomized Access (Part 1). The results are captured in Table 7 below.

Table 7. HFR Hospitalization Rates during the Full Period of Randomized Access (Part 1)

	Treatment (N=270)		Control (N=280)	
	# HFH	HFH Rate (HFH/pt-yr)	# HFH	HFH Rate (HFH/pt-yr)
Part 1	182	0.46	279	0.68

FDA Commentary 4: It is important to note that the effectiveness data from the Original PMA, which was presented at the previous panel meeting, was found to be confounded by subject-specific treatment recommendations made by nurses employed by CardioMEMS for Treatment group subjects. Therefore, FDA believes that the Longitudinal Analyses discussed in Sections 5.3.1 and 6.3.1 provide more appropriate analyses of the effectiveness data that is free of the confounding effects from the original efficacy analyses.

6.3 Longitudinal Analyses of HF Hospitalizations over Part 1 and Part 2

6.3.1 Longitudinal Analyses of HF Hospitalizations over Part 1 and Part 2 using Combined Data of Parts 1 and 2

There were 1498 total observations in the longitudinal analyses using combined data from Part 1 and Part 2. Among the 1498 observations, there were 603 events and 895 censored cases, and some subjects had multiple events. In this analysis, death was considered as a censoring event. The results of the individual comparisons are discussed below.

FDA Commentary 5: As noted above in FDA Commentary 2, it is important to note that these analyses are considered ancillary. Although p values are presented along with the results, caution should be used when interpreting them because the study was not

powered for these analyses, multiple analyses were conducted on the same data, and preservation of Type I error was not attempted.

1. Comparison of Former Control (Part 2) to Control (Part 1)

Comparison of the HFR hospitalization rates between Former Control (Part 2) and Control (Part 1) was an attempt to assess whether providing PA pressure information, in the absence of nurse communications, led to a lowering of HFR hospitalization rates. If the effect of HFR hospitalization rate observed in Part 1 was primarily due to use of the PA pressures, one would expect the HFR hospitalization rate in Control group subjects to decrease after the transition from Part 1 to Part 2. Shown in Table 8 and Table 9 below, the rate of HFR hospitalization decreased from 0.68 HFR hospitalizations per patient year for Control subjects in Part 1 to 0.36 HFR hospitalization per patient year for Former Control subjects in Part 2 (HR 0.52, $p < 0.0001$).

Table 8: Comparisons of HF Hospitalization Rates using Andersen-Gill Model with Frailty

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

Table 9: Number of Subjects, HFR Hospitalizations, and HFR Hospitalization Rates

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

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

FDA Commentary 6: FDA has reviewed the sponsor's statistical methods and parameters for these analyses and finds that they appear to be adequate.

2. Comparison of Former Treatment (Part 2) to Treatment (Part 1)

This analysis was an assessment of whether knowledge of PA pressure was responsible for the observed reduction in the rate of HFR hospitalization during the course of Part 1. If the effect on HFR hospitalization observed in Part 1 Treatment subjects was primarily due to use of the PA pressures, then continuing to use PA pressures to drive treatment decisions, and discontinuing nurse communications in Part 2, should result in a maintenance of the reduced HFR hospitalization rate observed in Part 1 after the

transition from Part 1 to Part 2. Shown in Table 8 and Table 9 above, the rate of HFR hospitalizations was similar for Treatment subjects (0.48 HFR hospitalization per patient year) in Part 1 and for Former Treatment (0.45 HFR hospitalization per patient year) in Part 2 (p= 0.5838).

3. Comparison of Former Control (Part 2) and Former Treatment (Part 2)

The observed difference in HFR hospitalization rates between the Treatment and Control groups in Part 1 should gradually decrease over time during Part 2 since PA pressures were used in subject management in both groups in Part 2. The sponsor performed two comparisons with results shown in Table 8 and Table 9 above**.**

1. Direct Comparison of Former Control to Former Treatment
   The rate of HFR hospitalizations for Former Control subjects (0.36 HFR hospitalization per patient year) was not shown to be different from the HFR hospitalization rate for Former Treatment subjects (0.45 HFR hospitalization per patient year) (p = 0.2178). However, the HFR hospitalization rate point estimate of the Former Control subjects is smaller than the HFR hospitalization rate point estimate of the Former Treatment subjects.

2. Comparison of Former Control vs. Former Treatment in Part 2 to Control vs. Treatment in Part 1
   The ratio of the group rates (Former Control / Former Treatment) in Part 2 was 0.80 (0.36/0.45= 0.80). The ratio of the group rates (Control / Treatment) in Part 1 was 1.42 (0.68/0.48 = 1.42). The ratio is approximately half as large in Part 2 than in Part 1 (p=0.0040) indicating the convergence of the HFR hospitalization rates for the two groups.

The hypothesis that Former Control subjects, with their therapy guided by PA pressures in Part 2, should demonstrate similar outcomes over time when compared to the Treatment Group (Part 1 and Part 2) was discussed during meetings between the sponsor and FDA. Based on the results of the comparison, it appears that the HFR hospitalization rates for the two groups began to converge.

4. Change in HF Hospitalization Rates in the Control group (Part 2 vs. Part 1) vs. the Change in HF Hospitalization Rates in the Treatment group (Part 2 vs. Part 1)

The sponsor compared the change in the Control group to the change in the Treatment group from Part 1 to Part 2 to account for longitudinal confounders across the two groups. The change in the rate of HFR hospitalization in the transition from Part 1 to Part 2 in the Control group (HR = 0.52) was greater than the change in the rate of HFR hospitalization from Part 1 to Part 2 in the Treatment group(HR = 0.93) (p=0.0040) as shown in Table 8 and Table 9 above.

6.3.2 Supporting Analyses

The sponsor conducted the following supporting analyses to complement the longitudinal analyses described in Section 6.3.1.

1. *Evaluation of the Anderson-Gill model Assumptions*
2. *Evaluation of Robustness of the Anderson-Gill model*
3. *Longitudinal Analysis using individual data*
4. *Analyses considering Competing Risks*
5. *Covariate-adjusted Longitudinal Analysis of HF Hospitalization Rates*
6. *Evaluation of Missing Data*

The first supporting analysis validates the assumptions used in the Anderson-Gill Model. The results of the other analyses are consistent with the results of the analyses described in Section 6.3.1. One exception was that using the Negative Binomial Regression for individual data (Supporting Analyses 3), the Former Control cohort had a lower HFR hospitalization rate than the Former Treatment cohort (HR is 0.84 with 95% CI (0.74-0.95) and p-value=0.0047); while all other analyses indicated no difference in the HFR hospitalization rate between the two groups. For details regarding these supporting analyses, please refer to Appendix A.

FDA Commentary 7: The results of all the longitudinal analyses were consistent with the primary endpoint analysis for Part 1 of the study. They suggest:

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

The impact of the treatment is a reduction of the HFR hospitalization rate by 0.20-0.32 per patient-year.

However, these results should be interpreted with caution, due to the following limitations:

1. *these are ancillary analyses;*
2. *the potential inequality of baseline covariates and demographics at the onset of Part 2 of the study; and*
3. *non-random subject drop-outs.*

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

In Question #2, the Panel will be asked to comment on the totality of these clinical data and whether all the analyses, taken together along with the limitations of each, demonstrate that the device is effective in reducing HFR hospitalizations in the intended patient population.

6.4 CLINICAL ANALYSIS RESULTS

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

Table 10: Concordant Medication Changes Within 1, 2, 3, or 7 Days of a Nurse Communication.

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

* One email ([redacted] on 7-29-08) led to 2 concordant changes (nitrate & ACE inhibitor) within 1-day window during 1st 6 months
^ One email ([redacted]2 on 7-7-08) led to 2 concordant changes (hydralazine & ACE inhibitor) within 7-day window during 1st 6 months
# One email ([redacted] on 6-12-08) led to 2 concordant changes (Nitrate & HDZ) within 7 day window during 1st 6 months

As seen in Table 10 above, there were 10 concordant changes not consistent with the study protocol and hypothesis. Four of these changes were considered to be clinically trivial. Based on the results of large-scale clinical trials and using conservative assumptions, the total effect of the 6 concordant changes not consistent with the study protocol and hypothesis would have been to prevent approximately 0.73 hospitalizations for heart failure during the first 6 months of randomized access in the subjects randomized to the Treatment Group. The observed difference in the number of HFR hospitalizations between the two Groups during the first 6 months of randomized access

was 36. Therefore, during the first 6 months of randomized access, the cardiologists estimated that approximately 2.0% (0.73/36) of the treatment effect may have been related to nurse communications that recommended changes not consistent with the study protocol and hypothesis.

Additionally, if adjustments are made for the background rate of use, the cardiologists estimated that approximately 0.9% (0.33/36) of the treatment effect seen during the first 6 months of randomized access may have been related to nurse communications that recommend changes in diuretics and nitrates. If all concordant medication changes are considered together, the cardiologists estimated 1.06 (0.73 + 0.33) hospitalizations for heart failure, or 2.9% (1.06/36) of the observed treatment difference seen during the first 6 months of randomized access may have been related to nurse communications.

FDA Commentary 8:
Any intervention in the treatment group by the sponsor involving correspondences that had the potential to alter therapy (regardless of whether the alteration is consistent with the protocol) is considered by FDA to have the potential to introduce bias. The protocol was designed to assess the physician's ability to utilize PA pressure information and not the capabilities of the sponsor's nursing staff to monitor and correct physician directed therapy.

FDA reviewed the sponsor's Clinical Analysis Plan and results and believes the most valuable portion of this analysis is confirmation that no nurse communications containing subject-management recommendations were made during Part 2 of the study. This freed the Part 2 data from the confounding effects of the nurse communications present in Part 1 of the study. Although the clinical analysis suggests that the actual effect of nurse communications on the HFR hospitalization rate was small, the equation of nurse communications to the number of HFR hospitalizations is an estimate, and the actual number cannot be ascertained. The equation of the two cardiologists was based on a series of assumptions and published literature. FDA believes it is difficult, at best, to accurately estimate how many HFR hospitalizations were avoided by the nurse communications.

FDA believes that further elaboration or evaluation of impact of nurse interventions in Part 1 would provide minimal additional information relevant to the analysis regarding the effectiveness of this device as it would likely be used in a postmarket setting.

6.5 Propensity Score Analysis Results

The matched datasets were provided to an independent 3rd party data analysis center for outcome analyses. The datasets demonstrated a consistent reduction in the rate of HFR hospitalization in the TNNC as compared with the rate in the propensity-matched controls using negative binomial procedure over the 30 matched datasets.

Based on the 30 sets of matched data generated from the reduced propensity score (PS) model, the minimum reduction in the rate of HFR hospitalization observed from the 30

data sets is 47.8% (95% CI from 33.9% to 58.8%) and the maximum reduction in the rate of HFR hospitalization observed from the 30 data sets is 48.9% (95% CI from 35% to 59.8%) in the TNNC group as compared the rate in the Propensity-matched control group.

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

Additional models including Basic NBR, Basic Poisson, Scaled Poisson and Bootstrap generated similar findings.

FDA Commentary 9: The PS analysis demonstrated a consistent reduction in the rate of HFR hospitalization in the TNNC as compared with the rate in the propensity-matched controls using the Part 1 study data. Although these results are consistent with the original Part 1 analysis, and with the longitudinal analyses, FDA believes these results should be interpreted with caution.

Even though PS matching can balance observed baseline covariates between two groups, they cannot balance unmeasured characteristics and confounders. More specifically, FDA believes there is selection bias when matching patients between the TNNC and Control Groups. Subjects placed in the TNNC Group did not have a nurse communication. FDA presumes that these patients were healthy enough to not warrant a nurse communication. This potential non-random selection bias limits the conclusions that can be drawn definitively from the propensity score analysis. For this reason, FDA believes that the longitudinal analyses presented in Section 6.3 above are the most useful in terms of supporting the effectiveness of the device.

6.6 Gender Analysis Results

The sponsor believes that early death in the Control group females explained the interaction-by-gender that FDA identified in the NOAP letter. This can be seen in the red-dashed circle in Figure 15 below. The sponsor performed a composite of time to death or first HFR hospitalization using a Cox proportional hazard model in a competing risk analysis over Part 1 and the full duration of Part 1 plus Part 2. The sponsor also performed an Anderson-Gill Model with Frailty, Anderson Gill Model with Robust Sandwich Estimates (RSE) and Negative Binomial Regression using an endpoint of time to HFR hospitalization or death in Part 1 and Part 1+Part2. As seen in the gray rows in Table 11 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, FDA typically uses a p-value of 0.15 because the analysis is typically not powered appropriately. When considering a p-value of 0.15, there was some evidence of treatment-by-gender interaction in the competing risk analyses under the following models:

- AG Model with Frailty for Part 1

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

Table 11: The results of treatment-by-gender interaction under different 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

However, these analyses also indicate an HFR Hospitalization benefit in men but no such benefit in women. The results of AG Model with Frailty are shown below in Table 12.

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		
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		
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		
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		
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

Figure 14 and Figure 15 below depict the Freedom from HFR Hospitalization and Freedom from Death for Men and Women over the Full Randomized Period (Part 1).

Figure 16 below depicts the composite endpoint of Freedom from HFR Hospitalization or Death for Men and Women over the Full Randomized Period (Part 1). They illustrate the apparent difference in treatment effect by gender.

Figure 14: Freedom from HFR Hospitalization Over the Full Randomized Period (Part 1).

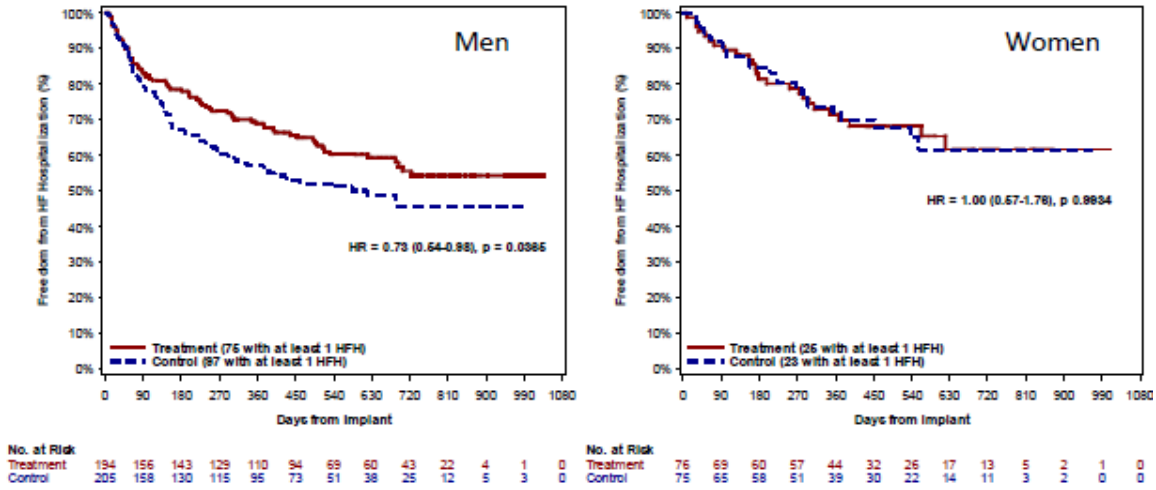


Figure 15. Freedom from Death Over the Full Randomized Period (Part 1).

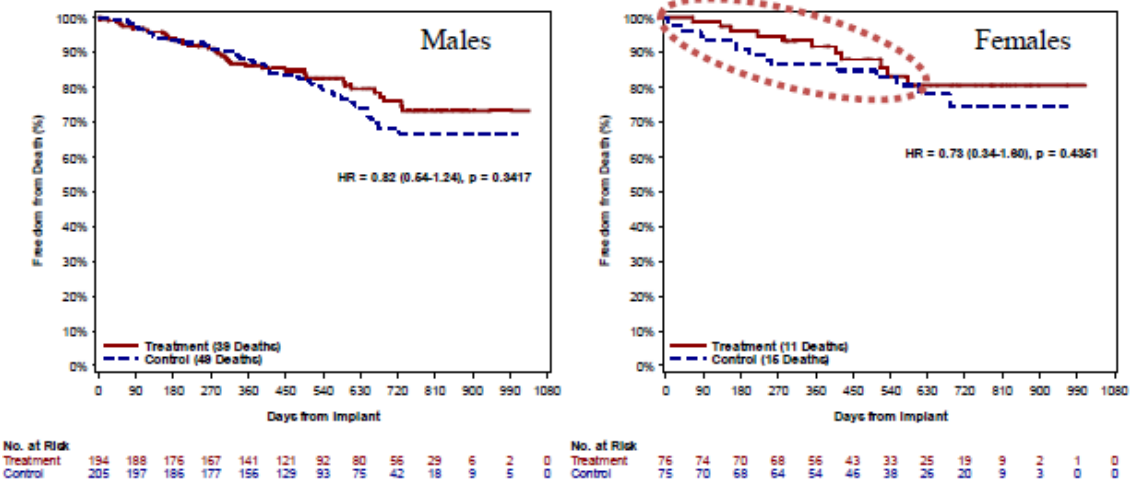
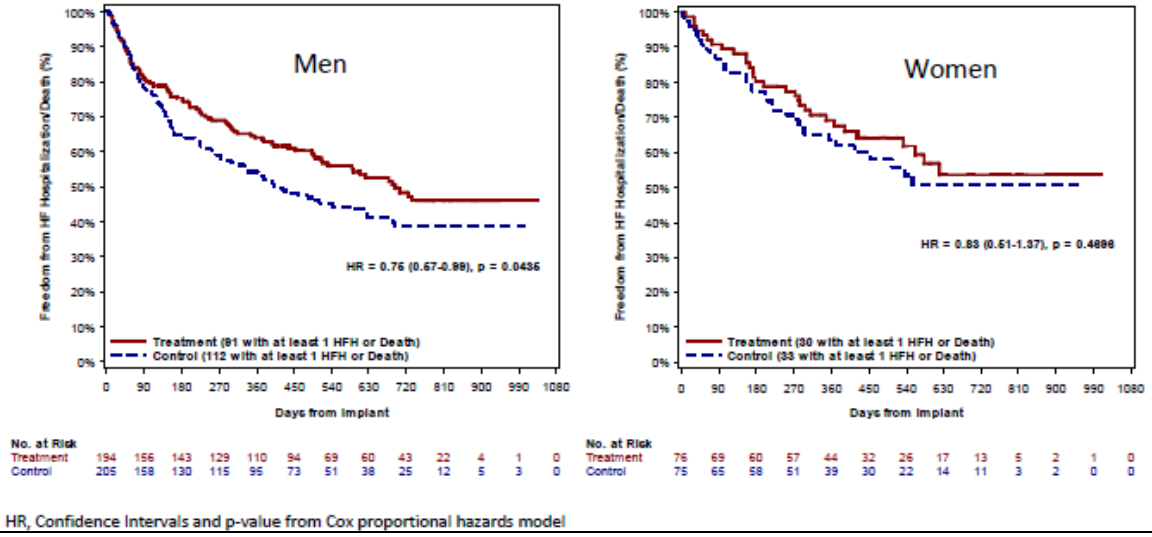


Figure 16. Freedom from HFR Hospitalization or Death Over the Full Randomized Period (Part 1).



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

FDA Commentary 10: After considering Death as event in the analysis, the gender-by-treatment interaction was not present using a p-value cutoff of 0.05. However, when considering a p-value of 0.15 commonly used by FDA for assessing treatment by gender interactions, there was some evidence of a treatment-by-gender interaction in multiple models.

There appears to be a limited treatment effect (HFR hospitalization rate reduction) in females. FDA is unclear whether this was due to the number of women in the study (N = 151) and few events in the trial or if it was due to the poor device efficacy among women. FDA believes that clarity should be sought by continuing to evaluate the treatment effect (HFR hospitalization rate reduction) in females in a proposed Post-approval Study if the device is recommended for approval.

In Question #3, the Panel will be asked to comment on the clinical significance of the Gender analysis and the treatment-by-gender interaction.

In Question #7 the Panel will be asked to consider whether this apparent limited effectiveness in females should be studied further as part of a post-approval study, should the device be approved.

6.7 Key Secondary Endpoints and Supplementary Analyses

The sponsor conducted a series of Secondary Endpoint and Supplementary Analyses as described above. Below are the results from the analyses that FDA believes are important in assessing the clinical significance of the observed results.

The sponsor analyzed the effect of the device on Quality of Life (QoL) using the Minnesota Living with Heart Failure Questionnaire (MLHFQ), as well as mortality over the entire study duration (Part 1 + Part 2). These analyses are tabulated in Table 13 and Table 14, and depicted in Figure 17 and Figure 18, respectively. A QoL benefit was noted

at 6 months; however, it did not appear to be sustained at 12 months. The mortality benefit was unaltered over the Part 1 (HR=0.80, p=0.23).

Table 13: Quality of Life: MLHFQ at 6 Months

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

Table 14: 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
Median	45.0	53.0	50.5	
(Min, Max)	(0.0, 100.0)	(0.0, 98.0)	(0.0, 100.0)	

Figure 17: Subject Survival over Part 1

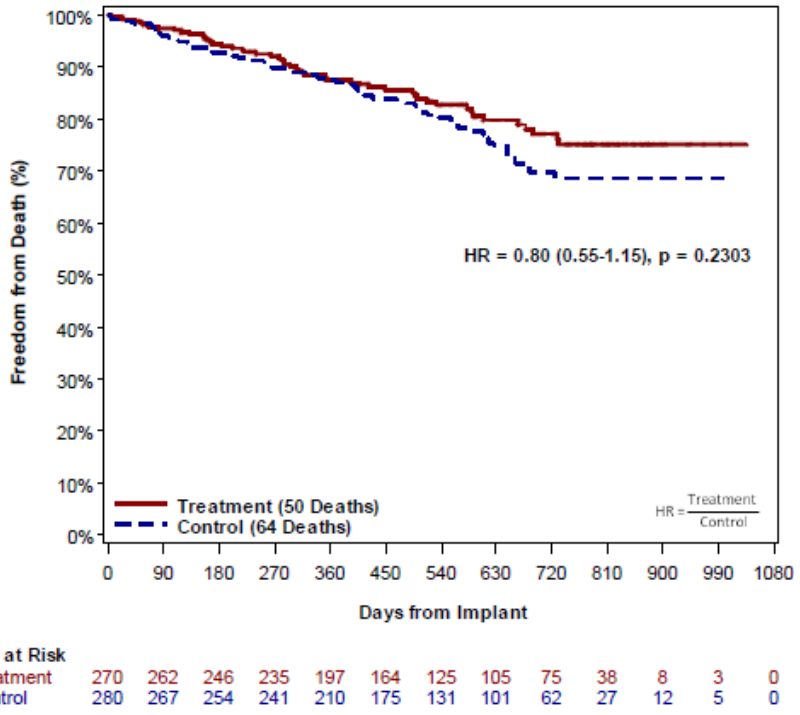
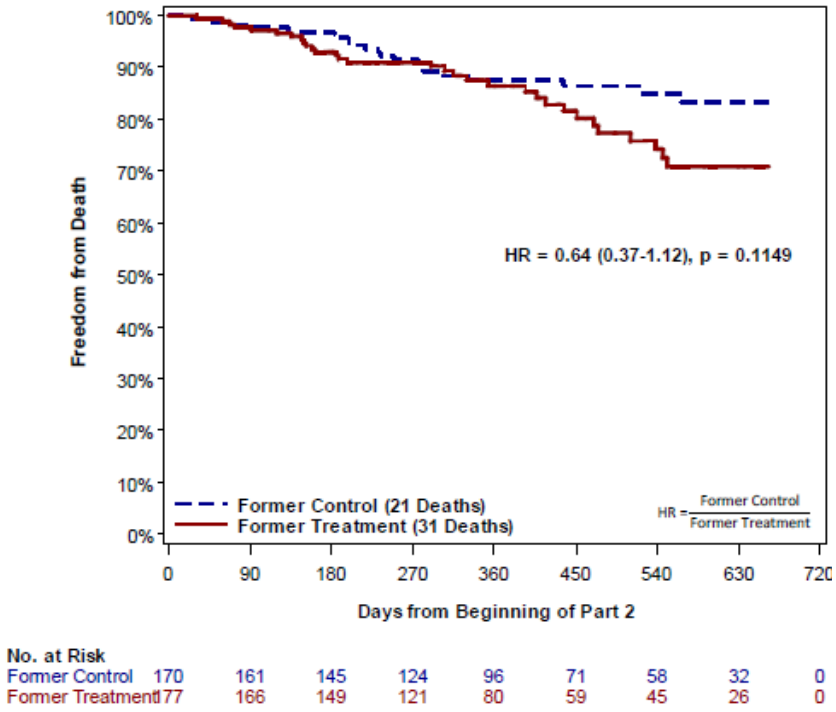


Figure 18: Subject Survival over Part 2



FDA Commentary 11: The absolute risk reduction in the proportion of subjects that experienced at least one HFR hospitalization was 8.6% and 7.7% at 12 and 24 months, respectively. HFR hospitalizations would be reduced by 20-32 HFR hospitalizations per 100 patients per year. The number needed to treat (NNT) to prevent one HFR hospitalization in a one year period is approximately 3-5. There was a noted QoL benefit in the Original PMA analysis at 6 months which did not appear sustained at 12 months. Despite the marked reduction in hospitalizations in the Treatment group, survival was unaltered over Part 1 (HR = 0.80, p=0.23).

In Question #2, the Panel will be asked to consider the clinical significance of the effectiveness results observed in the multiple analyses presented.

6.8 Safety Data

The panel previously reviewed the Safety Data for Part 1 of G060187 and voted that there was a reasonable assurance that the device is safe for the proposed indication.

In Part 2 of the study, there were no Unanticipated Serious Adverse Device Events, Serious Adverse Device Events, Non-Serious Adverse Device Events, or Device-System Related Complications. In addition, there were no sensor failures over the entire study duration (mean follow-up of 26 months, range: 1 day – 44 months).

FDA Commentary 12: The Safety Data for Parts 1 and 2 appears to be adequate. Additionally, the sensor performance over the course of the trial appears to be adequate.

7 Post-Approval Study

Note: The inclusion of a Post-Approval Study section in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for premarket approval and a recommendation from the Panel on whether the risks outweigh the benefits. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered. The issues noted below are FDA's comments regarding potential post-approval studies, for the Panel to include in the deliberations, should FDA find the device approvable based upon the clinical premarket data.

The FDA review team has made the recommendation that if the Champion™ HF Monitoring System is approved, a PAS should be required as a condition of approval for this device. Through review of Premarket Data, FDA has identified the following postmarket concerns and recommends that a PAS be conducted to assess:

1. the long term safety and effectiveness of this device in a real world general population;

2. the effectiveness of the training and education program for physicians in community hospitals; and

3. the safety and effectiveness of this device in subgroups, including gender, left ventricular ejection fraction (LVEF) groups, ischemic etiology, and with or without ICD/CRT-D.

The sponsor has not proposed a Post-approval Study in the most recent PMA Amendment.

FDA Commentary 13:
The sponsor has not proposed a Post-approval Study. FDA believes the following observations are pertinent for the Post-approval study.

Subject and investigator compliance is the key link between the device PA pressure readings and improved patient outcomes. The increased rate of subject non-compliance during the clinical trial raises questions of whether subjects will continue to comply with the device use requirements as time progresses following implantation. FDA believes that subject compliance with device use should be assessed as a secondary endpoint.

The required physician expertise and subject dedication in providing PA pressure readings to reduce HFR hospitalization is note-worthy. Additionally, the study sites selected for the CHAMPION study included both Academic and Community hospitals (Please refer to Appendix B for a list of study sites). FDA believes that physicians at Community hospitals may not be as equipped to manage patients with the Champion HF Monitoring System as those physicians at Academic hospitals. Therefore, FDA believes that there is a need to evaluate the training and education of physicians and to compare results between devices and patients followed at Academic and Community Hospitals in the Post-approval Study.

In Question #7, the Panel will be asked to comment on whether a series of questions, including the two mentioned above, should be addressed by a post-approval study.

8 Conclusions

No new safety data has been presented to change the assessment of the safety profile of the device. FDA continues to agree with the recommendations of the December 8, 2011 Panel who voted that the CardioMEMS device appears safe for its intended use.

A series of effectiveness analyses have been designed with FDA input and conducted. They all seem to be consistent with a device effect in reducing HFR hospitalization rates. However, every effectiveness analysis has its limitations and should be interpreted with caution as noted in the FDA Commentaries above.

The primary endpoint (the Part 1 effectiveness analysis) is confounded by the nurse communications. A third party audit of CardioMEMS nurse communications determined that there were no patient-specific treatment recommendations made by nurses during Part 2 of the study, thereby enabling additional statistical analyses to be performed on the Part 2 data. Although the third party audit and the conclusions reached by the cardiologists within the clinical analysis concluded that the effect of subject-specific nurse communications is minimal, it is difficult to know whether the underlying assumptions behind this analysis are valid.

The longitudinal analyses utilized the fact that PA pressure data was made available in Part 2 to the physicians of subjects randomized to the control arm in Part 1. Once PA pressure data became available, HFR hospitalization rates in those subjects decreased to levels comparable to the HFR hospitalization rates in treatment group subjects whose PA pressures were available throughout the study. However, baseline covariates were not

assessed at the start of Part 2 and there was an apparent difference in the study compliance and mortality rates between the control and treatment groups. Thus, it is unclear whether the subject populations in Part 2 of the study are comparable or if there is a systematic difference between them. Furthermore, because covariates at the baseline of Part 2 study are not available, it is not possible to evaluate:

a. if the subjects in Part 1 and Part 2 are comparable after subjects died and exited from the duration of Part 1;
b. if important covariates between the study groups remain balanced in Part 2;
c. if subjects in Part 2 continue to meet the trial inclusion/exclusion criteria; and
d. whether the difference in the clinical outcome may be confounded with differences in the subject populations.

The sponsor also conducted a propensity score analysis to compare HFR hospitalization rates among subjects who had not been the target of a CardioMEMS nurse communication. The sponsor identified a cohort of Part 1 treatment group subjects who had not been the target of a nurse communication. The Sponsor then used a propensity score model to match subjects in the Part 1 control group to that cohort. The results suggest that the device reduced HFR hospitalizations in subjects who had not been the target of nurse communications. However, the subjects in the treatment group who were not the target of a nurse communication are likely to represent the healthiest subjects in the Part 1 treatment group as there was no cause for CardioMEMS nurses to contact their physicians. This potential non-random selection bias limits the conclusions one can draw definitively from the propensity score analysis.

It is important to consider the totality of effectiveness data presented. Although each analysis on its own has its flaws and limitations, the consistency of the results are notable and should be considered when assessing whether the CardioMEMS device is effective.

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

While the statistical analyses appear to support the effectiveness of the device in reducing HFR hospitalizations, the clinical significance is less clear. The sponsor's secondary endpoints and supplementary analyses demonstrated a QoL benefit in the Original PMA analysis at 6 months, which did not appear sustained at 12 months, and that survival was unaltered over Part 1 despite the marked reduction in hospitalizations in the Treatment group. The NNT was determined to be 3-5 to avoid one hospitalization in the first year. FDA will ask the panel to comment on the fact that each patient requires a hospitalization for device implantation, coupled with the absence of a sustained QoL benefit at 12

months or increased survival benefit in the presence of reduced hospitalizations in the Treatment group.

FDA looks forward to a productive Panel discussion regarding these issues.

APPENDIX A: Longitudinal and Supporting Analyses Additional Details

Longitudinal Analyses Additional Details:

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

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

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

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

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

To assess the difference in heart failure hospitalization rate between treatment and control, the following four comparisons were performed:

1. Comparison of Former Control (Part 2) to Control (Part 1)
   The comparison of hazard ratio for Former Control to Control using X_1=0, X_2=1, X_3=0 vs. X_1=0, X_2=0, X_3=0 is the test of exp{β_2}. This is illustrated **Error! Reference source not found.** in **Error! Reference source not found.**.

2. Comparison of Former Treatment (Part 2) to Treatment (Part 1)
   The comparison of hazard ratio for Former Treatment to Treatment using X_1=1, X_2=1, X_3=1 vs. X_1=1, X_2=0, X_3=0 is the test of exp{β_2+ β_3}. This is illustrated **Error! Reference source not found.** in **Error! Reference source not found.**.

3. Comparisons of Former Control (Part 2) to Former Treatment (Part 2)
    a. Direct Comparison of Former Control to Former Treatment
    The comparison of hazard ratio for Former Control to Former Treatment using $X_1=0$, $X_2=1$, $X_3=0$ vs. $X_1=1$, $X_2=1$, $X_3=1$ is the test of $\exp\{-(\beta_1 + \beta_3)]$. This is illustrated **Error! Reference source not found.** in **Error! Reference source not found.**.
    b. Comparison of Former Control vs. Former Treatment in Part 2 to Control vs. Treatment in Part 1
    The comparison of two hazard ratio is the test of $\exp\{-(\beta_1 + \beta_3)\}/ \exp\{-\beta_1\} = \exp\{-\beta_3\}$.

4. Change in HF Hospitalization Rates in the Control group (Part 2 vs. Part 1) compared to the Change in HF Hospitalization Rates in the Treatment group (Part 2 vs. Part 1)
    The comparison of two hazard ratios is the test of $\exp\{\beta_2\} / \exp\{\beta_2 + \beta_3\} = \exp\{-\beta_3\}$. This is illustrated **Error! Reference source not found.** in **Error! Reference source not found.**.

In addition, the sponsor completed the following supporting analyses:

1. *Evaluation of Anderson-Gill model Assumptions (Proportional Hazards and Independence of the Recurrent Hospitalization).* The Proportional Hazards was assessed separately for Part 1 and over Part 1 + Part 2. Independence of recurrent hospitalization in Part 1 and in Part 2 was also evaluated.

2. *Evaluation of Robustness of Anderson-Gill model.* Additional evaluations included the use of non-parametric bootstrapping and Wilcoxon non-parametric procedures and parametric models including Negative Binomial and Poisson regression within a GEE model.

3. *Longitudinal Analysis using individual data.* Subgroup analyses using individual data sets for each comparison (1, 2 and 3a), i.e. the individual longitudinal comparison, were performed using Anderson-Gill model with Frailty and Negative Binomial Regression.

4. *Analyses considering Competing Risks.* Competing risks were considered using a composite endpoint of death or first HFR hospitalization in a Cox proportional hazard model and using Kaplan-Meier plots for Part 1 and Part 1+ Part 2. To accommodate multiple HF hospitalizations, the Anderson-Gill frailty model was used to evaluate multiple HFR hospitalizations or death (i.e. death was treated as an event).

5. *Covariate-adjusted Longitudinal Analysis of HFR Hospitalization Rates.* This analysis included clinically important baseline covariates in the Andersen-Gill model using the robust sandwich estimate: age, gender, systolic blood pressure, heart rate, estimated GFR, ejection fraction, cardiac index, mean PA pressure,

and diabetes mellitus.

6. *Evaluation of Missing Data.* Missing data for baseline covariates (3%) was imputed using multiple imputation procedures.

Supporting Analyses Additional Details:

1. *Evaluation of Anderson-Gill model Assumptions (Proportional Hazards and Independence of the Recurrent Hospitalization)*
   It was shown that proportional assumption and the independence of events assumption for Part 1 and for Part 2 was not violated.

2. *Evaluation of Robustness of Anderson-Gill model*
   The results of Poisson Regression within GEE model are presented in Table R, the results of Negative Binomial Regression within GEE model are presented in Table U. Table X shows the results of Wilcoxon Rank Sum Test and Tables KK presents the results of non-parametric bootstrap approach. All the results are consistent with the previous finding of the longitudinal analysis using AG model with Frailty in section 6.3.1

Table R. Longitudinal Analysis of HF Hospitalization Rates between Parts 1 and 2 Using GEE Poison Model

Comparison	Hazard Ratio (95% Confidence Interval)	p-value
1. Former Control to Control	0.56 (0.41 – 0.77)	0.0003
2. Former Treatment to Treatment	1.04 (0.77 – 1.41)	0.8002
3a. Former Control to Former Treatment	0.80 (0.52 – 1.22)	0.3046
3b. Former Control to Former Treatment vs. Control to Treatment	0.54 (0.34 – 0.83)	0.0057
4. Former Control to Control vs. Former Treatment to Treatment	0.54 (0.34 – 0.83)	0.0057
Results from repeated-measures GEE Model performing Poisson regression		

Table U. Longitudinal Analysis of HF Hospitalization Rates between Parts 1 and 2 Using GEE Negative Binomial Regression Model

Comparison	Hazard Ratio (95% Confidence Interval)	p-value
1. Former Control to Control	0.56 (0.40 – 0.79)	0.0009
2. Former Treatment to Treatment	0.91 (0.67 – 1.24)	0.5649
3a. Former Control to Former Treatment	0.80 (0.51 – 1.23)	0.3092
3b. Former Control to Former Treatment vs. Control to Treatment	0.62 (0.39 – 0.98)	0.0389
4. Former Control to Control vs. Former Treatment to Treatment	0.62 (0.39 – 0.98)	0.0389
Results from repeated-measures GEE Model performing Negative Binomial Regression		

Table X. Non-parametric Analysis of HF Hospitalizations using Wilcoxon Rank Sum Test

Comparison	Mean Difference	p-value	Total Events
1. Former Control to Control (n=170) [1]	0.565	**<0.0001**	224
2. Former Treatment to Treatment (n=177) [1]	0.136	0.2241	180
3a. Former Control to Former Treatment (n=347) [2]	-0.065	0.5125	142
3b. Former Control to Former Treatment vs. Control to Treatment (n=347)	N/A	N/A	N/A
4. Control to Former Control vs. Treatment to Former Treatment (n=347) [2] [3]	0.429	**0.0377**	404

[1] Wilcoxon Signed Rank test for within-group comparisons
[2] Wilcoxon Rank Sums test for between-groups comparisons.
[3] (Former Control minus Control) minus (Former Treatment minus Treatment)
N/A= Comparison 4a is a comparison between two between-groups tests and cannot be performed.

Table KK. Comparisons of Mean HF Hospitalization Rates from Nonparametric Bootstrapped Samples

Comparison	Mean HFH Rate* (HFH/pt.-year)	95% CI*
1. Former Control vs. Control (Part 2 - Part 1)	-0.351	**-0.518, -0.187**
2. Former Treatment vs. Treatment (Part 2 - Part 1)	-0.025	-0.180, 0.127
3. Former Control vs. Former Treatment (Part 2)	-0.093	-0.271, 0.082
4. (Former Control vs. Control) minus (Former Treatment vs. Treatment)	-0.326	**-0.551, -0.118**

HFH = Heart Failure Hospitalization
*Results based on empirical estimates from 10,000 samples of n=550 patients each

3. *Longitudinal Analysis using individual data*

Subgroup analyses using Anderson-Gill model with Frailty is presented in Table I and Table J below. The subgroup analyses using Negative Binomial is shown in Table GG.

Under the Anderson-Gill Model, there is a reduction in HF hospitalization rates from Control to Former Control (p = 0.0002) and no difference between Treatment and Former Treatment as well as between Former Control and Former Treatment, which is consistent with the previous finding in section 6.3.1. However, under the Negative Binomial Regression, it appears that Former Control has a lower HFR Hospitalization rates than Former Treatment (p-value=0.0047), while all other analyses show no difference in HFR Hospitalization rates between the two groups. This finding is not consistent with the results from all other longitudinal analysis models.

Table I. Comparisons of HF Hospitalization Rates using Model-based Estimates of Variance

Comparison	Hazard Ratio (95% Confidence Interval)	p-value
1. Former Control to Control	0.58 (0.43 - 0.77)	0.0002
2. Former Treatment to Treatment	1.04 (0.78 - 1.39)	0.7959
3a. Former Control to Former Treatment	0.82 (0.52 - 1.29)	0.3853
Results from Andersen-Gill Model with Frailty comparing HF hospitalization (HFH) rates		

Table J. Analysis Dataset Details

	Total Observations	Total Events	Total Censored Cases
1. Former Control to Control	791	343	448
2. Former Treatment to Treatment	707	260	447
3a. Former Control to Former Treatment	489	142	347

Table GG. HFR hospitalization rates comparison using Negative Binomial Regression

Comparison	HR (95% CI)	p-value
1. Former Control to Control	0.58 (0.42 - 0.81)	0.0012
2. Former Treatment to Treatment	0.88 (0.64 - 1.21)	0.4415
3a. Former Treatment to Former Treatment	0.84 (0.74 - 0.95)	0.0047

Results of 1 and 2 are from GEE Model performing Negative Binomial Regression

4. *Analyses considering Competing Risks*

The results (shown in Table XX) of Cox analyses considering the endpoint of first HFR hospitalization or death, and the results (shown in Table L) using Anderson-Gill Model with Frailty considering the endpoint of HFR hospitalization or Death demonstrated that there was a reduction in HF hospitalizations rates from Control to Former Control and no difference between Treatment and Former Treatment as well as between Former Control and Former Treatment.

Table XX. Comparison of HFR hospitalization rates using endpoint of first HFR hospitalization or death in a Cox proportional hazard model

Comparison	HR (95% CI)	p-value
1. Former Control to Control	0.53 (0.38 - 0.73)	<0.0001
2. Former Treatment to Treatment	0.85 (0.61 - 1.17)	0.3201
3a. Former Treatment to Former Treatment	0.83 (0.57 - 1.22)	0.3509

Table L. Comparisons of Event Rates (HFH or Death) using Andersen-Gill Model with Frailty

Comparison	Hazard Ratio (95% Confidence Interval)	p-value
1. Former Control to Control	0.61 (0.48 - 0.78)	<0.0001
2. Former Treatment to Treatment	1.09 (0.86 - 1.39)	0.4570
3a. Former Control to Former Treatment	0.76 (0.56 - 1.04)	0.0866
3b. Former Control to Former Treatment vs. Control to Treatment	0.56 (0.40 - 0.78)	0.0008
4. Former Control to Control vs. Former Treatment to Treatment	0.56 (0.40 - 0.78)	0.0008
Results from Andersen-Gill Model with Frailty comparing HF hospitalization (HFH)/Death rates		

Table M. Number of Patients, Events (HFH or Death) and Event Rates

	N	# Events	Event Rate (Event/pt-yr)
Treatment	270	232	0.61
Former Treatment	177	109	0.67
Control	280	342	0.84
Former Control	170	85	0.51
Results from Andersen-Gill Model with Frailty comparing HFH/Death rates			

Table N. Analysis Dataset Details – Part 1 and Part 2

Total Observations	Total Events	Total Censored Cases
1498	768	730

5. *Covariate-adjusted Longitudinal Analysis of HF Hospitalization Rates*
   Inclusion of clinically important covariates did not change the outcomes previously observed for these comparisons as shown in Table O below

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

Comparison	Hazard Ratio (95% Confidence Interval)	p-value
1. Former Control to Control	0.52 (0.36 - 0.74)	0.0003
2. Former Treatment to Treatment	0.94 (0.66 - 1.33)	0.7108
3a. Former Control to Former Treatment	0.83 (0.53 - 1.30)	0.4141
3b. Former Control to Former Treatment vs. Control to Treatment	0.55 (0.34 - 0.91)	0.0185
4. Former Control to Control vs. Former Treatment to Treatment	0.55 (0.34 - 0.91)	0.0185
Results from Andersen-Gill Model with using Robust Sandwich Estimates comparing HF hospitalization (HFH) rates		

6. *Evaluation of Missing Data*
   The baseline demographics are consistent before and after imputation.

APPENDIX B: List of Investigational Sites

Site Identifier	Investigator and Site Location	Number of Patients Consented	Number of Patients Enrolled
01	Philip Adamson, MD Oklahoma Heart Hospital, Oklahoma, OK	9	9
02	Ayesha Hasan, MD Ohio State University Hospital, Columbus, OH	15	13
03	Nicholas Chronos, MD Saint Joseph's Hospital, Atlanta, GA	14	12
04	Mark Aaron, MD Saint Thomas Hospital, Nashville, TN	16	15
05	Salpy Pamboukian, MD University of Alabama at Birmingham, Birmingham, AL	18	14
06	Suresh Neelagaru, MD Northwest Texas Hospital, Amarillo, TX	50	40
07	William Cotts, MD Northwestern Memorial Hospital, Chicago, IL	9	7
08	Steven Krueger, MD Bryan LGH Medical Center, Lincoln, NE	19	19
10	Gary Francis, MD University of Minnesota, Minneapolis, MN	8	8
11	Alan Niederman, MD Holy Cross Hospital, Fort Lauderdale, FL	7	6
12	Stan Weiner, MD Mother Frances, Tyler, TX	19	17
13	Amar Patel, MD Kennestone Hospital, Marietta, GA	11	10
14	Warren Strickland, MD Huntsville Hospital, Huntsville, AL	50	45
15	Barry Weinstock, MD Orlando Regional, Orlando, FL	15	15
16	Javier Jimenez, MD Mercy Hospital, Miami, FL	8	6
18	Daniel Bensimhon, MD Moses H. Cone Memorial, Greensboro, NC	11	10
19	William French, MD Harbor UCLA Medical Center, Los Angeles, CA	5	5
20	Brenda Hott, MD Northeast Georgia Heart, Gainesville, GA	5	4
21	Darrel Youngman, MD Via Christi Healthcare System, Wichita, KS	2	2
24	Fayaz Shawl, MD Washington Adventist Hospital, Takoma Park, MD	4	3

Site Identifier	Investigator and Site Location	Number of Patients Consented	Number of Patients Enrolled
26	AG Kfoury, MD Intermountain Healthcare LDS Hospital Salt Lake City, UT	5	4
27	Juan Aranda, MD Shands Hospital/ University of Florida, Gainesville, FL	8	7
29	Lee Goldberg, MD University of Pennsylvania, Philadelphia, PA	10	10
30	Orvar Jonsson, MD Sanford USD, Sioux Falls, SD	7	7
31	Michael Givertz, MD Brigham and Women's Hospital, Boston, MA	6	6
32	John Boehmer, MD Penn State Hershey, Hershey, PA	14	13
33	Alain Bouchard, MD Baptist Health – Princeton, Birmingham, AL	25	22
34	Mark Dorogy, MD Medical Center of Central Georgia, Macon, GA	5	5
35	Charles Parrott, MD Providence Hospital, Mobile, AL	12	11
36	Robert K. Strumpf, MD Arizona Heart Center, Phoenix, AZ	1	0
37	J. Tift Mann, MD Wake Med, Raleigh, NC	17	15
39	Steven Goldsmith, MD Hennipen County Medical Center, Minneapolis, MN	3	3
40	Kenneth Burnham, MD Spring Hill Medical Center, Mobile, AL	10	8
41	Tom Eagan, MD Trinity Medical Center, Birmingham, AL	13	12
42	Theodore Frank, MD Carolinas Medical Center, Charlotte, NC	1	1
43	Darshak Karia, MD Albert Einstein Medical Center, Philadelphia, PA	6	5
44	Frances Johnson, MD University of Iowa Healthcare, Iowa City, IA	14	14
45	Gregory Ewald, MD Barnes Jewish Hospital, St. Louis, MO	4	3
48	Barry Clemson, MD OSF Saint Frances Medical Center, Peoria, IL	1	1
49	Brain Jaski, MD Sharp Memorial, San Diego, CA	8	8
50	Pranav Loyalka, MD St. Luke's Heart Institute, Houston, TX	1	1

Site Identifier	Investigator and Site Location	Number of Patients Consented	Number of Patients Enrolled
51	Nirav Raval, MD Piedmont Hospital, Atlanta, GA	26	24
52	Guillermo Torre-Amione, MD Methodist Hospital, Houston, TX	5	5
53	Michael Mathier, MD University of Pittsburgh Medical Center Pittsburgh, PA	5	3
54	Ernest Haeusslein, MD California Pacific Medical Center, San Francisco, CA	3	3
55	Maria Constanzo, MD Edwards Hospital, Naperville, IL	24	18
56	Leonardo Clavijo, MD USC University Hospital, Loa Angeles, CA	7	6
57	Celeste Williams, MD Henry Ford Hospital, Detroit, MI	7	6
58	Michael Dickenson, MD Spectrum Health Research Dept, Grand Rapids, MI	2	2
59	Mark Riesman, MD Swedish General Hospital, Seattle, WA	4	3
60	David Shavelle, MD Good Samaritan Hospital, Los Angeles, CA	16	16
61	Michael Tuchek, MD Loyola University Research Center, Maywood, IL	2	0
62	Ed Garrett, MD Baptist Memorial Hospital, Memphis, TN	6	6
63	Eugene Simoni, MD Good Samaritan Hospital, Dayton, OH	4	4
64	Andrew Smith, MD Emory Hospital, Atlanta, GA	8	8
65	Donna Mancini, MD Columbia Presbyterian Center, New York, NY	3	3
66	Mark Silver, MD Advocate Christ Medical Center, Oak Lawn, IL	5	4
67	Ron Waksman, MD Washington Hospital, Washington, DC	1	1
68	G. Martin Mullin, MD Cardiovascular Associates, Elk Grove, IL	1	1
71	Raymond Benza, MD Allegheny General Hospital, Pittsburgh, PA	12	7
72	Roy Small, MD Lancaster General Hospital, Lancaster, PA	3	3
73	Ronald Freudenburger, MD Lehigh Valley Hospital, Allentown, PA	3	3

Site Identifier	Investigator and Site Location	Number of Patients Consented	Number of Patients Enrolled
74	Henry F. Fesniak, MD Geisinger Medical, Danville, PA	3	2
75	Thomas Nyggard, MD Centra Lynchburg General Hospital, Lynchburg, VA	2	2
76	Barry Berlot, MD North Mississippi Health Services, Tupelo, MS	5	3
81	Thomas Heywood, MD Sripps, La Jolla, CA	2	1