SUPPLEMENTAL MATERIAL

Supplemental Methods

Study Protocol

All subjects will be followed for 2 years. A subject is considered to have successfully completed the study upon completion of the 2-year visit.

During the screening visit, the following procedures/assessments will be performed to determine subject eligibility:

- Informed Consent prior to the conduct of any study-related procedures
- Physical examination including vital signs (temperature, heart rate, respiratory rate, blood pressure), weight, height, body mass index
- Medical and surgical history including ejection fraction data must be taken within the last 3 months
- Patient history of heart failure hospitalizations in the 12 months previous to the baseline visit as documented in information provided by the patient's cardiologist, internist, or referring physicians and review of all source documents of any heart failure hospitalization(s) reported in the previous year
- Demographics
- NYHA Functional Classification
- Calculation of glomerular filtration rate (GFR)
- Assessment of medications
- Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12)
- Brief Illness Perception Questionnaire
- Cardiac Health Security Survey
- Assessment of enrollment eligibility (inclusion/exclusion criteria)

The study coordinator or designee will administer patient-reported outcome questionnaires. It is important that the subject understands the meaning of all words and instructions in each questionnaire and answers all the questions. The subject will be instructed to ask any questions about the questionnaire if further explanation is needed. The research coordinator or designee will review the questionnaires to verify that all questions have been answered. The measures used will be the Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12), the Brief Illness Perception Questionnaire, and the Cardiac Health Security Survey. The Patient Reported Outcomes will be obtained at screening and each follow up visit post-implant (with the exception of the 1-month follow-up visit) for 2 years. Patients who were enrolled in the study prior to addition of patient reported outcome questionnaires, and therefore did not complete baseline questionnaires, are not required to complete questionnaires at the follow-up visits.

Eligible subjects will be scheduled for the Implant procedure. Subjects on anticoagulation therapy (e.g. warfarin) may be instructed by the Investigator to discontinue use 1-2 days prior to pressure sensor placement. The investigator should consider utilizing enoxaparin (Lovenox) per the site's standard of care as bridge therapy to Sensor placement in subjects who were on anticoagulation therapy. For subjects at risk for gastro-intestinal bleeding during the period in which dual antiplatelet therapy is given, the investigator should consider a proton pump inhibitor such as omeprazole (Prilosec). Subjects

at risk include the elderly, those with a history of gastroduodenal ulcers, gastroesophageal reflux disease, esophagitis, intestinal polyps or cancer. Subjects who smoke or who are using steroids or nonsteroidal anti-inflammatory drugs may also be at risk.

Right Heart Catheterization (RHC) and Implant Procedure (Baseline Visit)
Before the RHC, the following procedures/assessments will be performed:
- Abbreviated physical examination (i.e., vital sign assessments and significant changes since Screening Visit) and weight
- Confirmation of enrollment eligibility (other than angiographic criteria)
- PT/PTT with International Normalized Ratio (INR) of 1.5 or less for subjects previously on warfarin
- Assessment of heart failure medications
- Record any medical history updates since screening visit.

The patient will then undergo a standard RHC. A selective, hand injected pulmonary angiogram will be performed via the pulmonary artery catheter to identify a suitable pulmonary artery branch for sensor implantation. Subjects must have an appropriately sized (≥ 7mm diameter) pulmonary artery branch.

Subjects who do not meet this inclusion criteria will not receive the PA Sensor implant and will be considered ineligible for the study. These subjects will be documented as consented not implanted and will be followed for 30 days for safety. Patients with a suitable target pulmonary artery branch will undergo:
- Wireless implantable hemodynamic sensor implant
- Pulmonary artery catheter measurements (pulmonary systolic, pulmonary diastolic, pulmonary mean, cardiac output) done 3 times consecutively with sensor measurements for setting of sensor baseline.
- Provide post-procedure vascular access site care per standard procedure
- At the Investigator's discretion, subjects should be discharged once stable with respect to the procedure and their heart failure.
- Please see User's Manual for implant details

Subjects who are currently on anticoagulant therapy (warfarin, or any FDA approved anticoagulant) will restart treatment. The subject's INR should be checked periodically to ensure that it is in the therapeutic range. Those subjects not on chronic warfarin will be placed on anticoagulant/antiplatelet therapy as indicated in the device User's Manual.

Study Follow-Up Visits 1, 2, 3, 4, and 5 (Months 1, 6, 12, 18, and 24)
Implanted subjects will be evaluated at Month 1 (± 7 days) and at Months 6, 12, 18, and 24 (± 30 days) and the following procedures/assessments will be performed:
- Updated medical and surgical history
- Assessment of AEs that occurred since the last visit
- Abbreviated physical examination (significant changes since previous visit) including vital signs (heart rate, respiratory rate, blood pressure), and weight
- Assessment of NYHA functional class
- Kansas City Cardiomyopathy Questionnaire (KCCQ-12)
- Brief Illness Perception Questionnaire
- Cardiac Health Security Survey

- Heart failure medication review
- PA pressure measurements may be obtained at the Investigator's discretion

Subjects will be reminded to obtain pulmonary artery pressure measurements utilizing the CardioMEMS™ HF System as directed. Subjects will be reminded of the current ACC/AHA guidelines regarding sodium and fluid restrictions. The study coordinator or designee will administer patient-reported outcome questionnaires. It is important that the subject understands the meaning of all words and instructions in each questionnaire and answers all the questions. The subject will be instructed to ask any questions about the questionnaire if further explanation is needed. The research coordinator or designee will review the questionnaires to verify that all questions have been answered. The Patient Reported Outcomes will be obtained at 6, 12, 18 and 24 months. Patients who were enrolled in the study prior to addition of patient reported outcome questionnaires, and therefore did not complete baseline questionnaires are not required to complete questionnaires at the follow-up visits.

Subject Home PA Pressure Readings

Prior to hospital discharge, subjects will be instructed on how to take their own pulmonary artery pressure measurements, utilizing the CardioMEMS™ HF System. Subjects will provide returned demonstration on: setting up the unit, connecting the system to a phone line, proper positioning for obtaining the optimum sensor signal, taking and transmitting the daily pressure measurements. The unit will transmit the data to a database using the system's modem. The home measurements will be taken while the subject is lying down (supine) in bed positioned on a padded, flat antenna. It is recommended that subjects obtain home measurements in a supine position however, if the subject is unable to lie flat, measurements can be obtained in a sitting or reclined position. It is important the anatomical position is consistent for every measurement. The home electronics system is small enough for placement on a bedside table. The unit will provide audio and visual prompts for the subject to guide them through signal acquisition. Once the subject is positioned and a signal is acquired, the subject will be notified of the successful reading and the data is automatically transmitted to a remote database. St. Jude Medical will provide instructions for use and a help line will be available. Please refer to subject's Patient System Guide for more detailed information.

PA Pressure Readings in the Hospital

If a subject is hospitalized, seen in the emergency room (ER) or has a clinic visit, the CardioMEMS™ HF System may be used to obtain pulmonary artery pressure measurements at the investigators discretion. Following sensor implant, subsequent RHC procedures or pulmonary artery catheter insertions must be performed under fluoroscopic guidance. Resetting of the sensor baseline will be performed as deemed necessary by Sponsor. Baseline resetting may require an echocardiogram or a RHC procedure. Following the sensor implant, should a RHC procedure or PA catheter evaluation be clinically warranted, comparative pulmonary artery pressures utilizing the CardioMEMS™ HF System should also be obtained utilizing the hospital electronics unit.

Criteria for Withdrawal

Subjects may be withdrawn from the study for any of the following reasons:

1. Subject withdraws his/her consent ('withdrew consent').
2. Investigator determines that other treatment is warranted to protect the health and safety of the Subject ('terminated by investigator').
3. Investigator determines that the subject is noncompliant with study related procedures ('terminated by investigator').
4. Subject is lost to follow-up: site must document attempts made to contact the subject for an early

discontinuation visit (e.g., 2 – 3 phone calls, followed by 1 certified letter, documentation of repetitive missed study visits, etc.) ('lost to follow up').

5. Other – other reasons for withdrawal from study not classified into the above categories ('other').

The Investigator will notify the Sponsor and document on the appropriate case report form (CRF) the reason/circumstances for early discontinuation. All subjects who withdraw from the study should have the following study exit procedures performed if possible:

- Updated medical and surgical history
- Assessment of AEs that occurred since the last visit
- Abbreviated physical examination (only significant changes since Enrollment) including vital signs (temperature, heart rate, respiratory rate, blood pressure), and weight
- Assessment of NYHA functional class
- Kansas City Cardiomyopathy Questionnaire (KCCQ-12)
- Brief Illness Perception Questionnaire
- Cardiac Health Security Survey
- Heart failure Medication Review
- PA pressures may be obtained at the Investigator's discretion

All reasonable efforts should be made to retain subjects in the clinical trial until its completion. If a patient moves from the geographic area of their investigator, St. Jude Medical will attempt to place the patient with another investigator.

1   **Definitions for Hospitalization and Adverse Events**
2
3   Hospitalization – hospitalizations are defined as greater than or equal to 24 hours in a hospital (includes
4   admissions, emergency room visits, and observations). If time is not present or obvious then a calendar
5   date change will be utilized
6
7   Heart Failure – Patients must be admitted for heart failure or heart failure must be the primary reason
8   for hospitalization. Criteria must include both of the following:
9   A. Signs and symptoms of heart failure on hospitalization,

10   B. The use of intravenous diuretic, vasodilator, inotropic, or ultrafiltration therapy for the
11   purposes of treating heart failure. The augmentation of oral therapy may be allowable for
12   defining the hospitalization as heart failure, if no other reasonable diagnosis can be
13   attributed to the hospitalization.

14   Heart failure hospitalizations can be categorized into 2 major categories on the basis of
15   perfusion (adequate or inadequate). The inadequate perfusion group can then be
16   subdivided into 2 categories on the basis of volume.

17   1. Hypervolemia (Congestion):
18   Patients with signs and/or symptoms of congestion or volume overload. The most
19   frequent hospitalizations are for hypervolemic congestion, often referred to as "wet
20   and warm", these patients have adequate perfusion and cardiac output is relatively
21   preserved. These patients typically have elevated filling pressures or PCWP.
22   Therapy usually includes diuretics and vasodilators. These hospitalizations are
23   classified as Hypervolemic.

24   2. Low Output with Hypervolemia, Hypovolemia or Euvolemia:
25   a. Normal/Low volume: The low perfusion and normal or low volume patients,
26   often referred to as "cold and dry", are clinically manifested by the absence of
27   signs of congestion, no elevation of JVP, no edema, ascites, or rales. They
28   usually exhibit low BP, renal insufficiency, decreased urine output and possibly
29   decreased mentation. They are generally treated with fluids to raise filling
30   pressures in order to generate an adequate output and may also require
31   inotropes. These patients may cross over into "cold and wet" category after
32   they receive fluids.   These hospitalizations are classified as Low output with
33   normal or low volume.
34   b.   Volume Overload: The low perfusion and congested patients, often referred to
35   as "cold and wet", have a decrease in perfusion usually exhibited by low BP,
36   renal insufficiency, decreased urine output and possibly decreased mentation
37   with associated signs of congestion - volume overload, edema, rales. They are in
38   or near cardiogenic shock and usually require a combination of inotropes and
39   diuretics, as well as consideration for mechanical support (IABP, LVAD) and
40   possibly transplant. These hospitalizations are classified as Low output with
41   volume overload.
42   3. Complications of heart failure therapies:
43   a. Over diuresis – result of diuretics or any other therapy used in the treatment of
44   hypervolemia (i.e. ultrafiltration, dialysis, etc.)

b. Other – pharmacologically induced (i.e. ACE, ARB, Beta Blocker) complications or non-pharmacologic (i.e. CRT device complications, etc.)

Adverse Events (AE)

An AE is any untoward medical occurrence (e.g., noxious or pathological changes) in a subject compared with pre-existing conditions that may occur during any part of the clinical study. An AE is defined as being independent of assumption of any causality (e.g., primary or concomitant disease or study design).

Serious Adverse Event (SAE)

For this study, an SAE is defined as any untoward medical occurrence that: results in death, is immediately life-threatening – an event in which the subject was at risk of death at the time of the event, requires admission and hospitalization (> 24 hours) or prolongation of existing hospitalization, results in disability/incapacity, results in a congenital anomaly/birth defect, requires intervention to prevent one of the above. The cause of death of any subject after enrollment must be documented on the AE CRF and reported as an SAE. The information should include the date expired, cause of death, and what attempts were made to treat the condition.

Device-Relatedness

An AE or SAE that is definitely or possibly related to the device or the insertion procedure should be considered device-related. A serious adverse device effect (SADE) is an event that meets any of the above SAE criteria and is considered related to the device or the insertion procedure by the Investigator. All other events considered related to the device or insertion procedure are non-serious adverse device effects (ADEs).

Anticipated AEs

Events associated with the CardioMEMS™ PA Sensor or the implant procedure (in conjunction with RHC) or post-implantation complications are considered anticipated and include the following: infection, upper respiratory infection, bronchitis, pneumonia, acute bronchitis, groin abscess, methicillin-resistant staphylococcal aureus infection, pulmonary infiltration, sepsis, arrhythmias, ventricular tachycardia, atrial fibrillation, ventricular arrhythmia, ventricular fibrillation, atrial fibrillation with rapid ventricular response, atrial flutter, cardiac dysrhythmias, tachycardia, wide complex tachycardia, bleeding, epistaxis, hemoptysis, gastrointestinal bleed, bleeding, blood in stool, catheter site bleeding, catheter site ecchymosis, hematuria, nose bleeds, hematoma, catheter site hematoma, vessel puncture site hematoma, thrombus, arterial thrombosis (limbs), blood clot, myocardial infarction, transient ischemic attack, stroke, death, sensor embolization and pulmonary artery perforation.

Anticipated ADEs/SADEs

The following is a list of possible anticipated ADEs/SADEs: hemoptysis, sensor not deploying, transient ischemic attack, atypical chest pain, sepsis leading to death, atrial arrhythmia leading to death, arterial embolism (upper extremity), PA (in-situ) thrombus, catheter site bleeding, catheter site ecchymosis, catheter site hematoma, vessel puncture site pain, cardiac monitoring abnormal, heart rate irregular, serum creatinine increased, dyspnea, congestive heart failure, ventricular tachycardia, dizziness, vessel perforation, sensor failure/malfunction and sensor migration.

Other events

Pulmonary embolism – Pulmonary embolism will be diagnosed with confirmation by high probability V/Q scan, angiography, Spiral CT, or autopsy with or without acute onset of dyspnea, pleuritic chest pain, hypoxia, or hemodynamic dysfunction.

Pulmonary infarct – Radiographic evidence of pulmonary lesion diagnosed as infarction usually associated with pulmonary embolism

Myocardial Infarction – The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following: symptoms of ischemia; ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]); development of pathological Q waves in the ECG; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 x 99th percentile URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognized.
- For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 x 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction.
- In addition, the following general considerations will also be used to evaluate events with elevated troponins (Januzzi JL, *et al. Eur Heart J* 2012; 33, 2265–2271). Troponins should be interpreted within the context of the specific clinical presentation in which they are measured; in patients with HF, there are numerous causes for circulating troponin concentrations above the 99th percentile, including coronary and non-coronary mechanisms. The recognition of a troponin that is above the 99th percentile and its rising and/or falling does not absolutely indicate the presence of a Type I MI.

Coronary Insufficiency/Acute Coronary Syndrome/Unstable angina – Criteria must include all of the following: Ischemic symptoms upon presentation with hospitalization; cardiac markers not indicative of MI; treatment for acute coronary syndrome including some of the following: ASA, heparin, nitrates, GpIIb/IIa inhibitors, percutaneous coronary intervention, etc.; a positive diagnostic test for coronary artery disease or prior known history of CAD; a discharge diagnosis of acute coronary syndrome or unstable angina.

Atrial dysrhythmia – Typical ECG findings

Ventricular dysrhythmia – Typical ECG findings

Bradycardia/Heart block – Typical ECG findings

1 Syncope – classified as vasovagal, iatrogenic or other in etiology.

3 Stroke – Defined as a new, non-traumatic, primary focal neurological deficit that is sudden in onset,
4 thought to be vascular in origin, lasting at least 24 hours, and is ideally associated with CT or MRI
5 abnormalities of the brain.

7 Transient Ischemic Attack (TIA) – A transient ischemic attack is defined as a focal neurologic deficit,
8 presumed vascular in origin, which lasts for less than 24 hours, without new findings on CT, MRI. Any
9 new clinically relevant DWI MRI abnormality that cannot be confirmed by CT or T1/T2 MRI and is
10 associated with a focal neurological deficit lasting less than 24 hours is also classified as a TIA. A

12 Reversible Ischemic Neurological Defect (RIND) is also classified as a TIA. Post-seizure neurological
13 deficits will not be classified as a TIA.

15 Peripheral vascular disease – Hospitalization occurring from peripheral vascular disease or its
16 complications such as gangrene and extremity amputation. Does not include hypoperfusion of heart
17 failure.

19 Vascular embolism – Hospitalization occurring due to emboli to other vascular beds.

21 Aortic Aneurysm – Hospitalization occurring from a thoracic or abdominal aortic aneurysm or dissection
22 and supported by appropriate imaging data.

1 **Management of Hemodynamic Parameters**
2
3 The CardioMEMS™ HF System allows intermittent assessment of pulmonary artery (PA) systolic, diastolic
4 and mean pulmonary artery pressures. Hemodynamic information obtained by the system should be
5 used for clinical decision making in addition to symptoms, weights or physical examination (traditional
6 markers of volume). Normal PA pressure ranges are established as: PA Systolic 15 - 35 mmHg; PA
7 Diastolic 8 - 20 mmHg and PA Mean 10 - 25 mmHg.
8
9 Initially, thresholds will be set automatically at the acceptable range. The physician can adjust the
10 thresholds specifically for each patient. These threshold notifications are intended to guide the physician
11 to review the CardioMEMS™ HF Website. Every attempt should be made to keep the PA pressures
12 within the specified PA pressure ranges utilizing the guidelines. In order to clinically manage the
13 patient's PA pressures, the physician must review the PA pressure measurements on a frequent basis,
14 for example, some patients may require a daily review of their PA pressure measurements, while some
15 patients may need a weekly review. The physician or designee has unlimited access to the
16 CardioMEMS™ HF Website.
17
18 An elevation of pressures beyond the patient's pressure ranges should be considered a volume
19 overloaded status and should be managed according to the hyper-volemic guidelines (see below).
20 Diuretics and vasodilators should be adjusted based on the patient's baseline diuretic requirement,
21 knowledge of the patient's prior response to these agents, and clinician judgment to accomplish the
22 pressure goals set forth in this guideline. A decrease in the pulmonary pressures below the patient's
23 pressure ranges should be considered a volume depletion event and managed according to the hypo-
24 volemia guidelines (see below) (see below). Diuretic therapy should be held and the chronic dose should
25 be lowered. In addition to these specific guidelines, the physician should also incorporate the
26 recommendations set forth in the ACC/AHA 2013 Guidelines for the Diagnosis and Management of
27 Heart Failure in the Adult. The PA pressure readings should be used in addition to weights, signs and
28 symptoms, laboratory values and other traditional markers of volume in the management of heart
29 failure. It is important to review the trend of PA pressures. As with all other diagnostic information,
30 physicians should consider the entire medical history of each patient when initiating or modifying
31 therapies.
32
33 Elevated PA Pressures (Hyper-volemic)
34 Hyper-volemic Definitions
35 • Subject symptoms: Congestive symptoms (wet)
36 • CardioMEMS™ HF System Parameters: above the acceptable range
37 • Daily trends: elevated trend data outside the acceptable range
38 • Weekly trends: elevation in trend data
39
40 Treatment Recommendations
41 • Add or increase diuretic (and appropriate electrolyte replacement)
42 a. Increase or add loop diuretic
43 b. Change to another loop diuretic
44 c. Add thiazide diuretic (with caution)
45 d. IV doses of loop diuretic
46 e. Serum electrolyte evaluation with change in baseline medication
47 f. Re-assess pulmonary artery pressure utilizing the CardioMEMS™ HF System at least 2 – 3 days
48 per week until optivolemic

- Add or increase vasodilators including long-acting nitrates
- Re-educate in salt intake and fluid restriction
- If subject has signs and symptoms of poor perfusion (cold) in addition to being hypervolemic:
  a. Consider admission if clinical evidence suggests need for IV diuretics, telemetry monitoring or the IV therapeutic agents
  b. Consider invasive hemodynamic monitoring for determination of Cardiac Output, if indicated

Low PA Pressures (Hypo-volemic)

Hypo-volemic Definitions
- Subject symptoms: poor perfusion in absence of signs and symptoms of congestion
- CardioMEMS™ HF System Parameters: below the acceptable range
- Daily trends: decrease in trend data outside the acceptable range
- Weekly trends: decrease in trend data

Treatment Recommendations
- Lower or discontinue diuretic
  a. If on a thiazide diuretic with loop diuretic, lower or discontinue the dose of thiazide (and adjust electrolyte replacement)
  b. If on only loop diuretic, lower the dose or discontinue
  c. Consider liberalization of oral fluid restriction and salt restriction
- If postural hypotension, hold or lower vasodilators and/or oral nitrates, especially if hypotensive when sitting or supine
- If worsening renal function, hold or lower ACE/ARB dose, especially if hypotensive
- If subject had signs and symptoms of poor perfusion (cold) in addition to being hypovolemic:
  a. Consider admission if clinical evidence suggests need for IV fluid repletion, telemetry monitoring or the use of IV therapeutic agents
  b. Consider invasive hemodynamic monitoring for determination of Cardiac Output, if indicated

1 **Statistical Analysis Plan**
2
3 Data was summarized using univariate statistics (e.g., N, mean, standard deviation) or frequency (e.g., N,
4 %) as appropriate. The primary time point for safety analyses is 24 months post enrollment. Enrollment
5 was defined as having a successful sensor implant. The primary time point for effectiveness analyses was
6 12- months post enrollment. Unless otherwise specified, all statistical tests were 2-sided with a
7 significance level of 0.05.
8
9 Populations for Analysis
10 Safety Population: The Safety Population consists of all subjects who received a sensor implant or
11 underwent the implant procedure but were never implanted, regardless of study completion status. All
12 safety analyses were performed on the Safety population. Subjects who were found not to have an
13 appropriately sized pulmonary artery branch and did not receive the Sensor implant were considered
14 ineligible for the study. However, these subjects were followed for 30 days for safety and all safety
15 related data for these subjects is provided.
16
17 Effectiveness Population: The effectiveness population consists of all subjects who received a Sensor
18 implant regardless of study completion status. All effectiveness analyses were performed on the
19 effectiveness population.
20
21 Missing Data
22 Missing data was tracked in the Electronic Data Capture system. Queries were generated and
23 provided to the site. In addition, a St. Jude Medical representative, or designee routinely performed
24 monitoring visits at each site. During the monitoring visits, missing data queries were addressed until
25 resolution. Missing data that were not resolved were not imputed unless specified in the sections below.
26 Descriptive summaries were generated to describe the disposition of all enrolled subjects.
27
28 Safety Analyses
29 The safety analyses were performed using the Safety Population. The data was summarized using
30 univariate statistics (e.g., N, mean, standard deviation) or frequency (e.g., N, %) as appropriate.
31
32 Primary Safety Endpoints
33 The primary safety analyses was based on the following objective performance criteria: a) the lower
34 limit of the two-sided 95% confidence interval on the freedom from device / system-related
35 complication rate at 24 months is greater than 80% and b) the lower limit of the two-sided 95%
36 confidence interval on the freedom from pressure sensor failure rate at 24 months is greater than 90%.
37 These primary safety endpoints were tested hierarchically in order to control for multiplicity. First, the
38 freedom from device/system-related complication rate was tested. Given that the result was statistically
39 significant (i.e., p<0.050), the freedom from pressure sensor failure rate was tested for significance (i.e.,
40 p<0.050). Criteria for positive safety results were established if both tests of the primary safety analysis
41 endpoints were statistically significant (i.e., p<0.050).
42
43 Mathematically stated, the primary safety hypotheses were:
44 a) H0: P (Freedom from device/system-related complications at 24 months) ≤ 80%
45 Ha: P (Freedom from device/system-related complications at 24 months) > 80%
46 b) H0: P (Freedom from pressure sensor failure at 24 months) ≤ 90%
47 Ha: P (Freedom from pressure sensor failure at 24 months) > 90%
48 Plotting and analysis of safety endpoints will also be displayed using Kaplan-Meier methods.

Safety was also assessed throughout the study by the frequency of Adverse Events (AEs), Adverse Device Effects (ADEs), Serious AEs (SAEs), and Serious Adverse Device Effects (SADEs), and device/system-related complications by relationship to the device via Medical Dictionary for Regulatory Activities (MedDRA) system organ classification. Physical examination, and subject survival data through 12 months was tabulated across study period assessments.

Effectiveness Analyses

Effectiveness analyses were conducted in the effectiveness population. The data was summarized using univariate statistics (e.g., N, mean, standard deviation, median, minimum and maximum) or frequency (e.g., N, %) as appropriate.

Primary Effectiveness Endpoint

The primary time point for analyses was 12-months post-enrollment. The primary effectiveness endpoint was to compare the annualized HF hospitalization rate parameter, γ, at 1-year versus the HF hospitalization rate in the year prior to enrollment using a two-sample, two-sided Poisson confidence interval. Criteria to meet the primary effectiveness endpoint was established as two-sided, upper 95% confidence interval for the PAS rate parameter less than that in the year prior to enrollment.

Mathematically stated, the primary effectiveness hypothesis was:

H0: λ (12-month HF Hospitalization Rate) $\geq \lambda$ (HF hospitalization rate in year prior to enrollment)

Ha: λ (12-month HF Hospitalization Rate) $< \lambda$ (HF hospitalization rate in year prior to enrollment)

where λ (12-month HF Hospitalization Rate) = the HF hospitalization rate parameter at 1-year in the PAS and λ (HF hospitalization rate in year prior to enrollment) = the HF hospitalization rate in the year prior to enrollment.

Supplemental Analyses

In addition to the primary safety and effectiveness endpoints, several additional analyses were pre-specified as outlined below.

Mortality

Plotting and analysis of survival data will be displayed using Kaplan-Meier methods at 12 months.

Heart Failure Hospitalization (HFH) or Death

The annualized HFH or death rate parameter at 1 year was compared to the HFH rate in the year prior to enrollment using an Andersen-Gill method for recurrent events and robust sandwich variances to account for within-subject correlation. Criteria for the establishing the effectiveness endpoint was two-sided, upper 95% confidence interval for the hazard ratio (HR) less than 1.0.

Patient Compliance

Patient device usage over the course of the trial was examined. The total number of PAP readings taken were reported as a percentage of patient days at home.

Medication Changes in Response to PA Pressure

Medication changes in response to PA pressure on a per-subject basis and a per-medication changes basis were evaluated at 1-year follow-up.

Training Evaluation

To assess the effectiveness of the training program, the safety and effectiveness results were reported for: (1) Academic Hospitals and (2) Community Hospitals

Subgroup Analyses

The effectiveness analyses were evaluated in each of the following subgroups: (1) Women, (2) Men, (3) Reduced Ejection Fraction (< 40%), (4) Preserved Ejection Fraction (≥ 40%), (5) Ischemic Etiology, (6) Non-ischemic Etiology, (7) With ICD/CRT-D and (8) Without ICD/CRT-D

1 **Supplemental Tables**
2
3 Supplemental Table 1 below compares the characteristics of those that were withdrawn prior to 1-year
4 (n=79), those that did not survive to 1-year (n=187) and those that did survive to 1-year (n=934).
5
6 **Supplemental Table 1.** Baseline characteristics, medical therapy, baseline hemodynamics and
7 ambulatory hemodynamics in patients stratified by 1-year status.
8

	Withdrawn Prior to 1 Year N=76	Died Prior to 1 year N=186	Survived to 1 year N=938
Age, mean (SD), y	69 (14)	74 (10)	69 (12)
Men	52 (68.4)	137 (73.7)	557 (59.6)
Women	25 (31.6)	50 (26.7)	377 (40.4)
Race/ethnicity			
White	70 (88.6)	165 (88.2)	758 (81.2)
African American	6 (7.6)	16 (8.6)	150 (16.1)
Asian	0 (0.0)	3 (1.6)	9 (1.0)
Other	3 (3.8)	3 (1.6)	12 (1.3)
Ischemic cardiomyopathy	34 (43.0)	94 (50.3)	368 (39.4)
CRT or CRT-D device	17 (21.5)	45 (24.1)	177 (19.0)
ICD device	26 (32.9)	59 (31.6)	302 (32.3)
Comorbidities			
Hypertension	63 (79.7)	163 (87.2)	823 (88.1)
Coronary artery disease	52 (65.8)	141 (75.4)	599 (64.1)
Diabetes mellitus	43 (54.4)	105 (56.1)	507 (54.3)
Chronic obstructive pulmonary disease	32 (40.5)	61 (32.6)	329 (35.2)
Chronic kidney disease, Stage 3	40 (50.6)	124 (66.3)	530 (56.7)
Chronic kidney disease, Stage 4	12 (15.2)	27 (14.4)	75 (8.0)
Medical Therapy			
Beta blocker	66 (83.5)	160 (85.6)	831 (89.0)
ACE-I/ARB/ARNi	35 (44.3)	82 (43.9)	566 (60.6)
Beta blocker + ACE-I/ARB/ARNi	31 (39.2)	77 (41.2)	528 (56.5)
Aldosterone agonist	32 (40.5)	74 (39.6)	423 (45.3)
Loop diuretic	79 (100.0)	180 (96.3)	889 (95.2)
Glomerular filtration rate (mL/min/1.73m^2)	52.3 (23.1)	46.7 (19.8)	54.6 (21.0)
Baseline Hemodynamics at sensor implant			
Systolic blood pressure (mm Hg)	122.2 (22.0)	122.9 (21.6)	127.7 (22.1)
Heart rate (bpm)	75.0 (12.2)	73.7 (12.5)	73.8 (12.5)
Pulmonary capillary wedge pressure (mm Hg)	21.0 (9.9)	21.4 (8.4)	19.2 (8.1)
Pulmonary artery systolic pressure (mm Hg)	48.5 (15.6)	52.8 (15.7)	47.0 (14.5)
Pulmonary artery diastolic pressure (mm Hg)	21.1 (8.9)	21.5 (8.1)	19.7 (7.7)
Pulmonary artery mean pressure (mm Hg)	32.2 (10.5)	34.1 (10.4)	30.7 (9.6)
Cardiac index (Lit/min/m^2)	2.2 (0.8)	2.1 (0.7)	2.2 (0.7)
Ambulatory Hemodynamics during first week			
Pulmonary artery systolic pressure (mm Hg)	49.6 (12.7)	54.2 (13.6)	48.0 (13.7)

Pulmonary artery diastolic pressure (mm Hg)	25.4 (8.4)	27.1 (9.5)	24.2 (8.2)
Pulmonary artery mean pressure (mm Hg)	35.2 (9.9)	37.9 (10.4)	33.5 (10.1)

1 CRT- cardiac resynchronization therapy; CRT-D- cardiac resynchronization therapy defibrillation; ICD –
2 implantable cardiac defibrillator; ACE-I – angiotensin converting enzyme inhibitor; ARB – angiotensin
3 receptor blocker; ARNi – angiotensin receptor–neprilysin inhibitor.
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1 Supplemental Table 2 below compares the heart failure hospitalization (HFH) and all cause
2 hospitalization (ACH) 1-year pre implant and 1-year post-implant stratified by baseline mean pulmonary
3 artery pressures. Baseline pulmonary artery pressures were stratified as < 25 mm Hg, ≥ 25 mm Hg and <
4 35 mm Hg and ≥ 35 mm Hg. HFH 1-year post-implant were consistently lower compared to the 1-year
5 pre-implant, regardless of baseline mean PA pressure; all p values <0.0001.
6

7 **Supplemental Table 2**. Summary of heart failure hospitalization (HFH) and all cause hospitalization
8 (ACH) pre-implant and 1 year post-implant stratified by baseline mean pulmonary artery (PA) pressures.

	Baseline Mean PAP < 25 (N=211)	25 ≤ Baseline Mean PAP < 35 (N=435)	Baseline Mean PAP ≥ 35 (N=550)	All Subjects (N=1200)
HFH	0.978 vs. 0.295 [211] 0.30 (0.22, 0.41)	1.221 vs. 0.519 [435] 0.43 (0.36, 0.51)	1.374 vs. 0.649 [550] 0.47 (0.41, 0.54)	1.249 vs. 0.535 [1200] 0.43 (0.39, 0.47)
ACH	2.158 vs. 1.287 [211] 0.60 (0.48, 0.74)	2.263 vs. 1.586 [434] 0.70 (0.63, 0.79)	2.321 vs. 1.891 [550] 0.81 (0.74, 0.89)	2.277vs. 1.667 [1200] 0.73 (0.68, 0.78)

9 [1]Includes all CEC adjudicated Heart Failure hospitalizations with an admission date on the date of implant and through 390 days prior to date of
10 implant.
11 [2]Includes all CEC adjudicated Heart Failure hospitalizations with an admission date after the implant procedure discharge date through 390 days
12 after the date of implant.
13 [3]Hazard Ratio, 95% Confidence Interval, and p-value estimated from the Andersen-Gill model with robust sandwich estimates.
14 [4]Hospitalization Rate is an annualized rate estimated from the Andersen-Gill model.

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1 Supplemental Table 3 compares the heart failure hospitalization (HFH) pre implant and 1-year post-
2 implant stratified by the baseline number of HFHs pre-enrollment and stratified by ejection fraction. For
3 patients with ≥ 5 HFH pre-enrollment (n=21), there were 5.87 events/patient-years before compared
4 with 1.79 events/patient-years after implant, resulting in a risk reduction of 70% (HR 0.30, 95% CI 0.19,
5 0.48; p <0.0001). For patients with 2-4 pre-enrollment (n=349), there were 2.25 events/patient-years
6 before compared with 0.82 events/patient-years after implant, resulting in a risk reduction of 63% (HR
7 0.37, 95% CI 0.31, 0.43; p <0.0001). Patients with < 2 HFH pre-enrollment (n=830), there were 0.72
8 events/patient-years before compared with 0.39 events/patient-years after implant, resulting in a risk
9 reduction of 46% (HR 0.43, 95% CI 0.47, 0.62; p <0.0001).
10
11 Although the number of patients in the ≥ 5 HFH pre-enrollment group was small (n=21), these findings
12 suggest that the benefits of PA pressure guided therapy appear to be more significant for patients that
13 were more 'ill' at study entry (i.e. HFH pre-enrollment ≥ 5).

14 **Supplemental Table 3**. Summary of Change in Pre-Enrollment vs Readmission Heart Failure
15 Hospitalizations.

Number of HFH pre-enrollment	EF < 40% (N=637)	40% ≤ EF ≤ 50% (N=198)	EF > 50% (N=363)	All Subjects (N=1200)
Change in HFH by # of Admits < 2	0.730 vs. 0.462 [422] 0.63 (0.53, 0.76)	0.776 vs. 0.333 [139] 0.43 (0.29, 0.63)	0.702 vs. 0.316 [269] 0.45 (0.33, 0.61)	0.721 vs. 0.389 [830] 0.54 (0.47, 0.62)
2 to 4	2.273 vs. 0.838 [200] 0.37 (0.30, 0.45)	2.511 vs. 0.879 [57] 0.35 (0.25, 0.49)	2.208 vs. 0.838 [90] 0.38 (0.28, 0.52)	2.247 vs. 0.823 [349] 0.37 (0.31, 0.43)
≥5	6.104 vs. 2.070 [15] 0.34 (0.21, 0.55)	5.689 vs. 2.276 [2] 0.40 (0.20, 0.80)	6.345 vs. 0.643 [4] 0.10 (0.01, 0.76)	5.874 vs. 1.790 [21] 0.30 (0.19, 0.48)

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Supplemental Table 4. Investigators and Study Sites

Site Name	Primary Investigator
Sanford USD Medical Center	Jonsson, Orvar
Centracare Heart and Vascular Center	Pelzel, Jamie
St. Francis Hospital	Jermyn, Rita
Catholic Medical Center	Capodilupo, Robert
First Coast Cardiovascular Institute	Zuberi, Omer
University Hospitals Cleveland Medical Center	Robinson, Monique
Heart Hospital of Austin	Bhatt, Kunjan
Huntington Memorial Hospital	Rao, Vyshali
USC University Hospital	Shavelle, David
Providence Hospital	David, Shukri
Scripps Green Hospital	Heywood, Thomas
Aurora Sinai Medical Center	Sulemanjee, Nasir
Cardiovascular Institute of the South - Lafayette	Ayalloore, Siby
Minneapolis Heart Institute	Bennett, Mosi
University of Arizona	Juneman, Elizabeth
North Shore University Hospital	Stevens, Gerin
Ohio State University	Hasan, Ayesha
McLaren Health Care Corporation	Masri, Kalil
Methodist Hospitals Inc	Artis, Andre
Sharp Memorial Hospital	Jaski, Brian
Brigham and Women's Hospital	Givertz, Michael
Providence Heart and Vascular Institute	Abraham, Jacob
Ventura Cardiology Consultants	Kong, Thomas
Advocate Good Samaritan Hospital	Valika, Ali
Community Heart and Vascular	Safiia, Muhamad Adeeb
Genesis Medical Center	Rajendran, Vijayaraghavan
Piedmont Athens Regional Medical Center	Marti, Catherine
Mayo Clinic	Redfield, Margaret
University of Kentucky	Guglin, Maya
South Denver Cardiology Associates PC	Dauber, Ira
West Virginia University Hospital	Sokos, George
Mercy Medical Center	Kassiotis, Chris
NC Heart and Vascular Research	Jobe, R. Lee
University Hospital - Univ. of Alabama at Birmingham (UAB)	Tallaj, Jose
University of California at San Francisco	Selby, Van
Advocate Health and Hospitals Corporation	Costanzo, Maria Rosa
HealthCare Partners Cardiology	Ivey, Pamela
Hudson Valley Cardiovascular Practice, P.C.	Lyons, James
University of Miami Hospital	Chaparro, Sandra
Cedars-Sinai Medical Center	Czer, Lawrence

Site Name	Principle Investigator
Munson Medical Center	Recchia, Dino
Advanced Heart Care Associates	Spaccavento, Leo
Lancaster General Hospital	Roberts, Justin
Aspirus Wausau Hospital	Luetmer, Paul
Gundersen Lutheran Medical Center	Bird, Julio
Stamford Hospital	Hsi, David
Vidant Medical Center	Alhosaini, Hassan
Cardiac Rhythm Specialists, Inc.	Polosajian, Leo
East Tennessee Heart Consultants	Foster, Malcolm
Eisenhower Medical Center	Feldman, Leon
Heart Rhythm Specialists	McKenzie, John
Swedish Medical Center - Heart & Vascular	Mignone, John
Vanderbilt University Medical Center	Schlendorf, Kelly
Heart Care Centers of Illinois - Palos Park	Macaluso, Gregory
King's Daughters Medical Center	Van Deren, John
Mayo Clinic Scottsdale	Hardaway, Brian
Northeast Ohio Cardiovascular Specialists	Costantini, Ottorino
Northshore University HealthSystem	Gordon, Robert
Penn State Milton S. Hershey Medical Center	Boehmer, John
The Cardiac & Vascular Institute Research Foundation, LLC	Tong, Ann
University of Colorado Hospital	Altman, Natasha
Renown Regional Medical Center	To, Thomas
Arizona Arrhythmia Research Center	Swarup, Vijendra
Atlantic Health System - Morristown Memorial Hospital	Goldschmidt, Marc
John C. Lincoln North Mountain Hospital	Seifert, Mark
Northwestern Memorial Hospital	Anderson, Allen
Ochsner Medical Center	Ventura, Hector
The Lindner Center	Egnaczyk, Gregory
Fairview Southdale Hospital	Jama, Abdi
Heart Center Research, LLC.	Murphy, James
Kansas University Medical Center	Sauer, Andrew
Mercy Hospital St. Louis	Czarnik, Bruce
Scott & White Memorial Hospital	Hicks, Albert
Spartanburg Regional Medical Center	Rodak, David
Spectrum Health Butterworth Hospital	Dickinson, Michael
Sutter Medical Center, Sacramento	Xu, Zi-Jian
The Reading Hospital and Medical Center	Green, Jared
Torrance Memorial Medical Center	Shin, Victoria
Abington Memorial Hospital	Watson, Robert
Allegheny General Hospital - ASRI	Benza, Raymond
Barnes-Jewish Hospital	Vader, Justin

Site Name	Principle Investigator
Covenant HeathCare	Jundi, Mayar
Gwinnett Medical Center	Lipsitt, Michael
Hoag Memorial Hospital Presbyterian	Itchhaporia, Dipti
Massachusetts General Hospital	Thomas, Sunu
Mount Sinai Hospital	Moss, Noah
Albany Medical College at Albany Med. Ctr.	Philbin, Edward
Florida Hospital	Raval, Nirav
Huntsville Cardiovascular Clinic	Strickland, Warren
Lehigh Valley Hospital - 17th Street	Islam, Nauman
Main Line Health Center/Lankenau Hospital	Droogan, Christopher
Medical City Dallas Hospital	Chemmalakuzhy, Jacob
Medical University of South Carolina	Steinberg, Daniel
New Jersey Cardiology Associates	Rubenstein, Donald
California Pacific Medical - Ctr. Pacific Campus	Herr, Jared
Centennial Medical Center	Johnston, Thomas
Hawaii Pacific Health	Kao, John
LSU Health Sciences Center	Dominic, Paari
Presbyterian Hospital	McMillan, Edward
Rapid City Regional Hospital	Heilman, K
Sutter Gould Medical Foundation - Briggsmore Spec. Center	Tsai, Charles
The Cleveland Clinic Foundation	Jacob, Miriam
Winthrop-University Hospital	Marzo, Kevin

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