SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	System, Hemodynamic, Implantable
Device Trade Name:	CardioMEMS™ HF System
Device Procode:	MOM
Applicant's Name and Address:	St. Jude Medical (Abbott) 387 Technology Circle NW Suite 500 Atlanta, GA 30313
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P100045/S056
Date of FDA Notice of Approval:	

The original PMA (P100045) was approved on May 28, 2014 and is indicated for wirelessly measuring and monitoring pulmonary artery pressure and heart rate in New York Heart Association (NYHA) Class III heart failure patients who have been hospitalized for heart failure in the previous year. The hemodynamic data are used by physicians for heart failure management and with the goal of reducing heart failure hospitalizations. The SSED to support the indication is available on the CDRH website (http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100045B.pdf) and is incorporated by reference here. The current supplement was submitted to expand the indication for the CardioMEMS HF System to include NYHA Class II or Class III patients who either have been hospitalized for heart failure in the previous year and/or have elevated natriuretic peptides in the previous 30 days.

II. INDICATIONS FOR USE

The CardioMEMS HF System is indicated for wirelessly measuring and monitoring pulmonary artery pressure and heart rate in NYHA Class II or III heart failure patients who either have been hospitalized for heart failure in the previous year and/or have

elevated natriuretic peptides. The hemodynamic data are used by physicians for heart failure management with the goal of controlling pulmonary artery pressures and reducing heart failure hospitalizations.

III. CONTRAINDICATIONS

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

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

The CardioMEMS™ HF System provides pulmonary artery (PA) hemodynamic data used for monitoring and management of heart failure (HF) patients. The system measures PA pressure and the data are used by the physician to proactively manage HF patients and initiate or modify heart failure treatment.

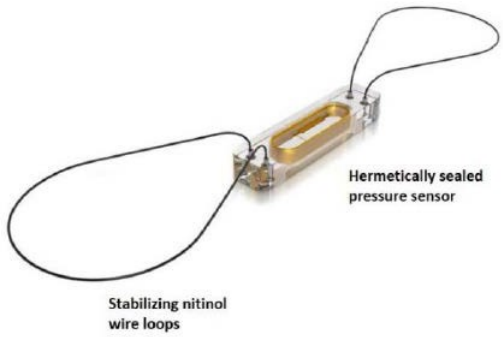
The CardioMEMS HF System consists of the following components:

- PA Sensor and Delivery System
- Hospital Electronics System
- Patient Electronics System
- Heart Failure Web Application (Merlin.net)

The wireless sensor (Figure 1) is designed for permanent implantation into the distal pulmonary artery. Once implanted, the CardioMEMS PA Sensor provides non-invasive hemodynamic data that are collected in the physician's office, clinic, hospital, or patient's home. The data provided by the system includes:

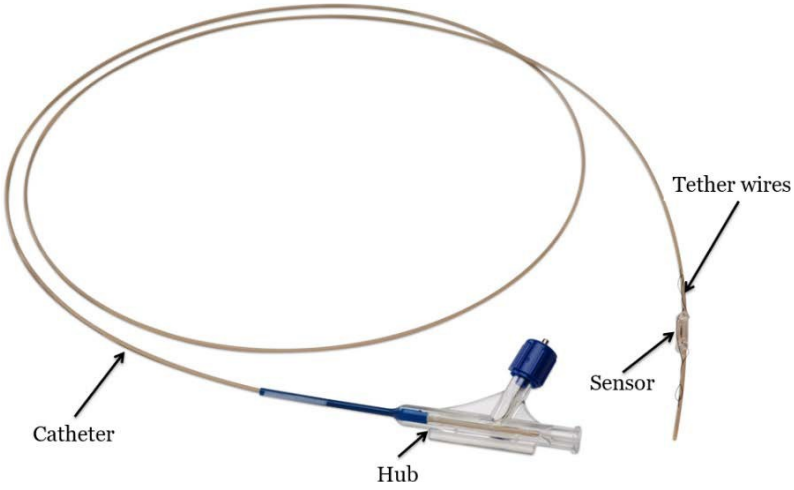
- PA pressure waveform
- Systolic, diastolic, and mean PA pressure
- Heart rate

Figure 1: Pulmonary Artery Sensor



The sensor is provided mounted on the distal end of an endovascular delivery catheter, as shown in Figure 2.

Figure 2: PA Sensor and Delivery System



This hemodynamic data are transmitted by the Hospital Electronics System (Figure 3) and Patient Electronics System (Figure 4) to a secure website that serves as the patient database so that PA monitoring information is always available through the internet. Changes in PA pressure can be used in conjunction with heart failure signs and symptoms to guide adjustments to medications.

Figure 3: Hospital Electronics System

Figure 4: Patient Electronics System

VI. ALTERNATIVE PRACTICES AND PROCEDURES

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

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

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

VII. MARKETING HISTORY

The CardioMEMS HF System is commercially available in the following countries: Argentina, Australia, Austria, Belgium, Canada, Colombia, Denmark, France, Germany, Ireland, Italy, Netherlands, Portugal, Spain, Switzerland, United Arab Emirates, United Kingdom, and United States of America.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- Air embolism
- Allergic reaction due to device component materials or procedure related
- Infection
    - Upper respiratory infection
    - Bronchitis
    - Pneumonia
    - Acute Bronchitis
    - Groin abscess
    - Methicillin-resistant staphylococcal aureus infection
    - Pulmonary Infiltration
    - Sepsis

- Delayed wound healing
- Arrhythmias
    - Ventricular tachycardia
    - Atrial fibrillation
    - Ventricular arrhythmia
    - Ventricular fibrillation
    - Atrial fibrillation with rapid ventricular response
    - Atrial flutter
    - Cardiac dysrhythmias
    - Tachycardia
    - Wide complex tachycardia
    - Atrial dysrhythmia
- Bleeding
    - Epistaxis/Nose bleeds
    - GI bleed
    - Bleeding - Other
    - Blood in stool
    - Catheter site bleeding
    - Catheter site ecchymosis
    - Hematuria
- Hemoptysis
- Hematoma (Bruising)
    - Hematoma
    - Catheter site hematoma
    - Vessel puncture site hematoma
- Nausea
- Cerebrovascular accident
    - Stroke/Transient ischemic attack
- Thrombus
    - Arterial thrombosis (limbs)
    - Blood clot
- Cardiovascular Injury
    - Vascular rupture
    - Valve damage
    - Pseudoaneurysm formation
    - AV Fistula
    - Pulmonary artery injury
- Myocardial infarction (Heart attack)
- Death
- Embolism
    - Pulmonary infarct
    - Pulmonary embolism
    - Device embolization
- Thermal Burn
- Cardiac Perforation

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

IX. SUMMARY OF NONCLINICAL STUDIES

Nonclinical studies that were summarized in the Summary of Safety and Effectiveness for the original PMA (P100045) are equally applicable to the expanded Indications for Use. A summary of the previously reported nonclinical studies can be found in the SSED for the original PMA (http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100045B.pdf).

X. SUMMARY OF PRIMARY CLINICAL STUDY

GUIDE-HF Trial - Randomized Arm

The applicant performed a clinical study in the US under IDE#G170258 to establish a reasonable assurance of safety and effectiveness of the CardioMEMS HF System to guide the treatment of patients with New York Heart Association (NYHA) Class II - IV heart failure. Data from this clinical study were the basis for the current PMA supplement approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were enrolled from 3/15/2018 to 12/20/2019. The database for the Panel Track Supplement reflected data collected through Jan 18, 2021 and included 1007 patients from 114 U.S. sites and 15 patients at 4 sites in Canada.

The study was a prospective, randomized, controlled, single-blind, multicenter, pivotal clinical trial. The study enrolled subjects with NYHA Class II, III, or IV heart failure and either elevated natriuretic peptides (N-terminal pro-B-type natriuretic peptide [NT-proBNP] or B-type natriuretic peptide [BNP]) and/or a prior HF hospitalization. All enrolled subjects underwent a right heart catheterization and implantation of a CardioMEMS device. Successfully implanted subjects were then randomized 1:1 to either hemodynamic-guided management using information provided by the CardioMEMS HF System (Treatment group) or heart failure management according to the standard of care (Control group). All patients took daily readings from home, but they were blinded to the treatment assignment or PA pressure measurements. Clinicians had access to pulmonary artery pressure information for patients in the Treatment group but not for patients in the Control group. Patient contacts were performed with scripted calls and equalized between two groups.

The study was evaluated for success based on the composite of HF hospitalization,

urgent HF visits (emergency department or hospital outpatient visits for intravenous diuretic therapy), and all-cause mortality at 12 months. The study would be considered successful by demonstrating that the hemodynamic-guided HF treatment is superior to the control therapy for heart failure outcomes.

An independent Clinical Events Committee (CEC) provided blinded adjudication for all primary endpoint events. An independent Data Safety Monitoring Board (DSMB) oversaw clinical data and safety.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the GUIDE-HF Trial (Randomized Arm) was limited to patients who met the following inclusion criteria:

   1) Diagnosis and treatment for HF (regardless of LVEF) for > 90 days prior to the date of consent:
      Subjects should be on stable, optimally titrated medical therapy for at least 30 days, as recommended according to current AHA/American College of Cardiology (ACC) guidelines as standard-of-care for HF therapy in the United States, with any intolerance documented.
   2) NYHA Class II, III or IV HF symptoms documented within 30 days prior to consent.
   3) HFH within 12 months prior to consent and/or elevated NT-proBNP (or BNP) within 30 days prior to consent defined as:
      a. Subjects with LVEF ≤ 40%: NT-proBNP ≥ 1000 pg/mL (or BNP ≥ 250 pg/mL).
      b. Subjects with LVEF > 40%: NT-proBNP ≥ 700 pg/mL (or BNP ≥ 175 pg/mL).
      c. Thresholds for NT-proBNP and BNP (for both LVEF ≤ 40% and LVEF > 40%) will be corrected for BMI using a 4% reduction per BMI unit over 25 kg/m^2 *
   4) ≥ 18 years of age
   5) Chest circumference of < 65 inches, if BMI is > 35 kg/m^2
   6) Written informed consent obtained from subject
   7) Willing and able to upload PA pressure information and comply with the follow-up requirements

   Patients were not permitted to enroll in the GUIDE-HF Trial (Randomized Arm) if they met any of the following exclusion criteria:

   1) Intolerance to all neuro-hormonal antagonists (i.e., intolerance to angiotensin converting enzyme-inhibitors (ACE-I), angiotensin receptor

blockers (ARB), angiotensin-neprilysin inhibitors (ARNi), *and* beta-blockers)

2) ACC/AHA Stage D refractory HF (including having received or currently receiving pharmacologic circulatory support with inotropes)
3) Received or are likely to receive an advanced therapy (e.g., mechanical circulatory support or cardiac transplant) in the next 12 months
4) NYHA Class IV HF patients with:
    a. Continuous or chronic use of scheduled intermittent inotropic therapy for HF and an INTERMACS level of ≤ 4, OR
    b. Persistence of fluid overload with maximum (or dose equivalent) diuretic intervention
5) Glomerular Filtration Rate (eGFR) < 25 mL/min and non-responsive to diuretic therapy, or receiving chronic dialysis
6) Inability to tolerate or receive dual antiplatelet therapy or anticoagulation therapy for one month post-implantation
7) Significant congenital heart disease that has not been repaired and would prevent implantation of the CardioMEMS PA Sensor
8) Implanted with mechanical right heart valve(s)
9) Unrepaired severe valvular disease
10) Pregnant or planning to become pregnant in the next 12 months
11) An active, ongoing infection, defined as being febrile, an elevated white blood cell count, on intravenous antibiotics, and/or positive cultures (blood, sputum or urine).
12) History of current or recurrent (≥ 2 episodes) pulmonary emboli and/or deep vein thromboses
13) Major cardiovascular event (e.g., unstable angina, myocardial infarction, percutaneous coronary intervention, open heart surgery, or stroke, etc.) within 90 days prior to consent
14) Implanted with Cardiac Resynchronization Therapy (CRT)-Pacemaker (CRT-P) or CRT-Defibrillator (CRT-D) for less than 90 days prior to consent
15) Enrollment into another trial with an active treatment arm
16) Anticipated life expectancy of < 12 months
17) Any condition that, in the opinion of the Investigator, would not allow for utilization of the CardioMEMS HF System to manage the subject using information gained from hemodynamic measurements to adjust medications, including the presence of unexpectedly severe pulmonary hypertension (e.g., trans-pulmonary gradient >15) at implant RHC, a history of non-compliance, or any condition that would preclude CardioMEMS PA Sensor implantation.

*Thresholds for NT-proBNP and BNP (for both LVEF ≤ 40% and LVEF > 40%) were corrected for BMI using a 4%

reduction per BMI unit over 25 kg/m^2 per the Frankenstein equation.

2. Follow-up Schedule

All randomized patients were scheduled to return for follow-up examinations at 6 and 12 months. Adverse events and complications were recorded at all visits.

The key timepoints are shown in Table 1 summarizing schedule of treatments and evaluations.

Table 1. Schedule of Treatments and Evaluations

Visit Trial Activity	Baseline (up to -60 days)	Implant (time zero)	Prior to Discharge	Phone Contact[1] (Randomized Arm Only)	6 Months (+/-14 days)	12 Months (+/-30 days)
Informed Consent Process	X					
Assessment of Inclusion/Exclusion Criteria	X					
Demographic Information	X					
Cardiovascular History	X					
BMI (and Chest Circumference if BMI > 35kg/m^2)	X					
Limited Echo for EF (if no EF documented)	(X)					
EQ-5D-5L and KCCQ-12 Administration	X				X	X
Creatinine and Calculation of eGFR	X				X	X
NT-proBNP (or BNP)	X				X	X
Medication Review and Documentation	X		X		X	X
HF Exam (Including NYHA Assessment)	X				X	X
6MHW Test	X				X	X
CardioMEMS™ HF System Information		X				
Catheterization Laboratory PA Pressure Measurements		X				
Randomization (Randomized Arm Only[2])			X			
Subject Teaching / Compliance Assessment			X	X	X	X
Subject Contact Worksheet				X		
Medication Update Documentation		(X)	(X)	(X)	(X)	(X)
Reportable AEs	(X)	(X)	(X)	(X)	(X)	(X)
Protocol Deviation	(X)	(X)	(X)	(X)	(X)	(X)
Non-AE Device Issues		(X)	(X)	(X)	(X)	(X)
Death	(X)	(X)	(X)	(X)	(X)	(X)

(X) If applicable/as it occurs

[1]All sites will be required to be in contact with each subject in the Randomized Arm (including subjects in the Treatment and Control Groups) at least once every two weeks during the first three months from the date of implantation and then at least once per month from three months to the 12 month follow-up visit.

[2]Randomization should be completed as soon as possible but within 24 hours of implant, and prior to discharge.

3. Clinical Endpoints

With regards to effectiveness, the primary endpoint is a composite of the following:

- Hospitalization (≥ 24 hours) with the primary reason for admission being acute decompensated HF and intravenous administration of diuretic therapy
- An unscheduled or unplanned admission to the emergency department, hospital outpatient observation visit, or hospital inpatient visit and intravenous administration of diuretic therapy
- All-cause mortality.

With regards to safety, the secondary safety endpoint is freedom from Device or System Related Complications (DSRCs) at 12 months post-implantation.

DSRC was defined as an adverse event that was related to or possibly related to the system (wireless pressure sensor or external electronics) and had at least one of the following characteristics:

- Treated with invasive means (other than intramuscular medication or an RHC used for diagnostic purposes)
- resulted in the death of the subject
- resulted in the explant of the device

With regard to success/failure criteria, study success was defined as demonstrating superiority for the primary endpoint hypotheses below at a significance level of 2.5%:

H_0: Hazard ratio (HR) for the Composite Endpoint at 12 months (Treatment to Control) ≥ 1
H_1: HR for the Composite Endpoint at 12 months (Treatment to Control) < 1

or

$H_0: e^{\beta 1} \geq 1$
$H_1: e^{\beta 1} < 1$

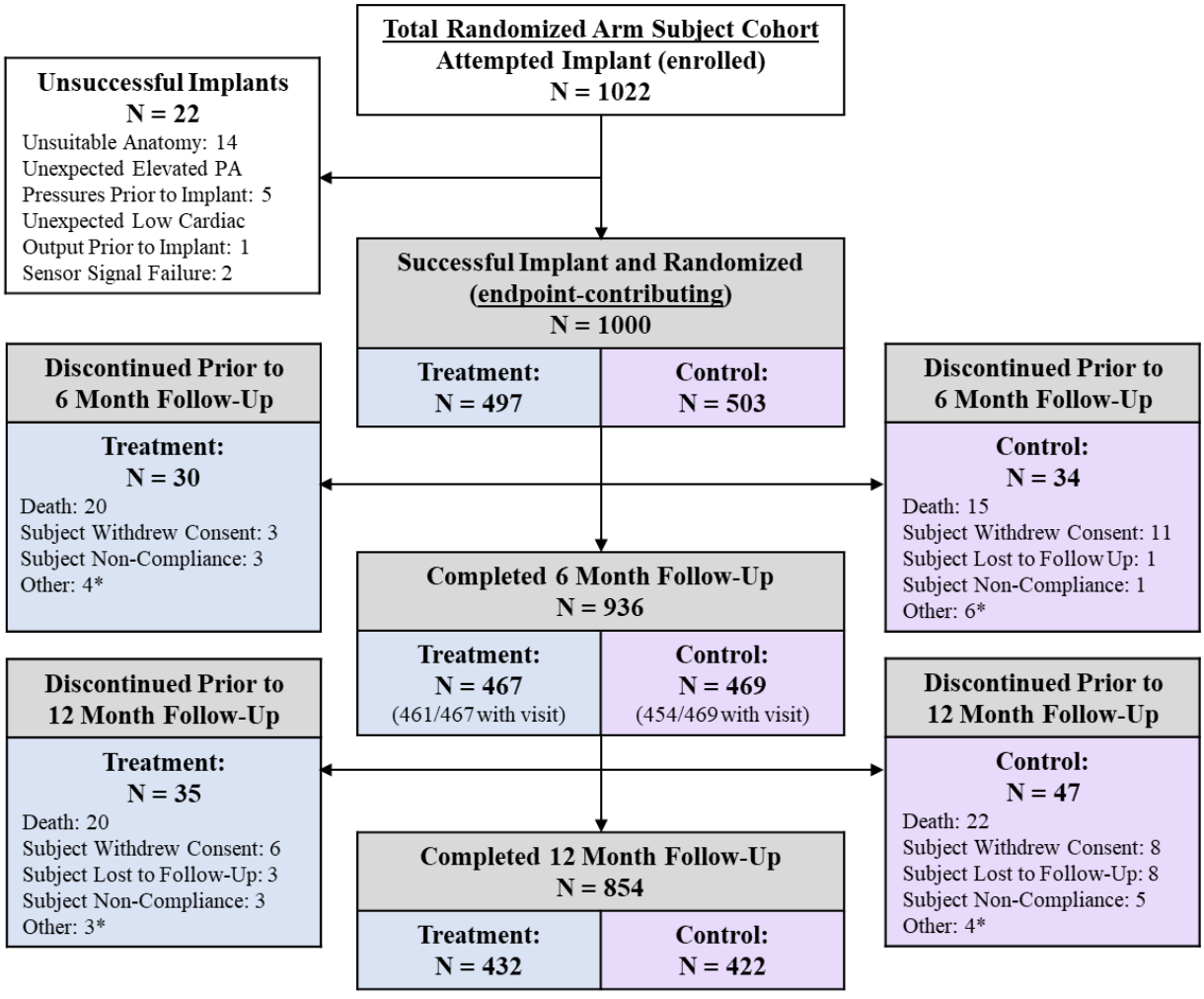
where e is the exponential function and β1 is the regression coefficient obtained from the covariate representing randomized group (Treatment or Control) in the Andersen-Gill model. Thus, the hazard ratio is the exponentiation of the regression coefficient for randomized group. This is equivalent to testing the regression coefficient against zero.

All randomized subjects were included in the analysis population.

B. Accountability of PMA Cohort

A total of 1022 patients were consented for trial enrollment and underwent a right heart catheterization and implantation of a CardioMEMS device. Of these, 22 did not receive an implant, primarily due to anatomical/physiological conditions identified during the right heart catheterization. The observed PA sensor implant success rate was 97.8%. The remaining 1000 subjects who received a successful implant were randomized 1:1 to either the Treatment group (N = 497) or the Control group (N = 503). At the time of database lock, 854 (85.4%) randomized subjects completed the 12-month follow-up visit. Figure 5 summarizes the subject disposition in the PMA study:

Figure 5. Subject Disposition



The protocol specified the following analysis populations:
Endpoint Analysis Population: All randomized subjects (N = 1000)
Safety Population: All enrolled subjects (N = 1022)

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a heart failure study that enrolls NYHA Class II-IV patients in the US. The mean age was 69.2 ± 11 years and 37.5% were female. NYHA II, III, and IV patients account for 29.6%, 65.0%, and 5.4% of the randomized subjects. Table 2 presents the demographics and patient characteristics by randomized group. The Treatment and Control groups were balanced in all relevant demographics and baseline characteristics.

Table 2. Subject Demographics and Characteristics (Endpoint Analysis Population)

	Treatment (N=497)	Control (N=503)	p-value[1]
Age - year	69.2 ± 11.1 (497)	69.2 ± 11.0 (503)	0.8996
Female Sex	37.6% (187/497)	37.4% (188/503)	0.9480
Race			
White	81.1% (403/497)	80.5% (405/503)	0.8725
Black	17.5% (87/497)	18.5% (93/503)	0.7420
Asian	0.0% (0/497)	0.2% (1/503)	1.0000
American Indian or Alaskan Native	0.4% (2/497)	0.4% (2/503)	1.0000
Pacific Islanders	0.0% (0/497)	0.0% (0/503)	
Other	1.2% (6/497)	0.6% (3/503)	0.3389
Ethnicity			
Hispanic	3.2% (16/497)	3.4% (17/503)	1.0000
Non-Hispanic	96.0% (477/497)	96.0% (483/503)	1.0000
Unknown	0.8% (4/497)	0.6% (3/503)	0.7241
Body mass index - kg/m^2	32.9 ± 8.3 (497)	33.8 ± 8.4 (503)	0.0571
NYHA Class			
II	29.4% (146/497)	29.8% (150/503)	0.8900
III	64.8% (322/497)	65.2% (328/503)	0.8947
IV	5.8% (29/497)	5.0% (25/503)	0.5778
Medical History			
Ischemic etiology	41.6% (207/497)	37.8% (190/503)	0.2198
Previous myocardial infarction	29.0% (144/497)	31.4% (158/503)	0.4093
Previous percutaneous coronary intervention	33.2% (165/497)	31.4% (158/503)	0.5885
Previous coronary artery bypass grafting	27.2% (135/497)	27.0% (136/503)	1.0000
Diabetes	48.9% (243/497)	51.9% (261/503)	0.3759
Cerebrovascular accident	13.3% (66/497)	12.9% (65/503)	0.9254
Atrial flutter or fibrillation	60.4% (300/497)	57.9% (291/503)	0.4404
Vital Signs and Hemodynamic Analyses			
Heart rate - bpm	73.8 ± 12.5 (497)	74.2 ± 12.3 (503)	0.7438
Systolic blood pressure - mmHg	121.6 ± 19.1 (497)	120.8 ± 18.1 (503)	0.6134
Diastolic blood pressure - mmHg	69.2 ± 10.8 (497)	69.0 ± 10.8 (503)	0.7996
Left ventricular ejection fraction - %	39.4 ± 17.3 (497)	40.7 ± 16.9 (503)	0.1870
Left ventricular ejection fraction > 40%	45.1% (224/497)	48.7% (245/503)	0.2546

	Treatment (N=497)	Control (N=503)	p-value[1]
Pulmonary artery systolic pressure - mmHg	44.9 ± 13.9 (497)	45.2 ± 14.6 (503)	0.9194
Pulmonary artery diastolic pressure - mmHg	18.9 ± 8.0 (497)	18.8 ± 7.7 (503)	0.8203
Pulmonary artery mean pressure - mmHg	29.2 ± 9.5 (497)	29.4 ± 10.0 (503)	0.9631
Pulmonary capillary wedge pressure - mmHg	17.3 ± 8.0 (495)	17.6 ± 7.9 (503)	0.6171
Cardiac output - L/min	4.83 ± 2.62 (497)	4.70 ± 1.46 (503)	0.8459
Cardiac index - L/min/m^2	2.27 ± 1.11 (497)	2.19 ± 0.63 (503)	0.4609
Ambulatory Hemodynamics during First Week			
Pulmonary artery systolic pressure - mmHg	46.3 ± 14.4 (497)	46.2 ± 13.3 (499)	0.7640
Pulmonary artery diastolic pressure - mmHg	22.4 ± 7.8 (497)	22.7 ± 7.4 (499)	0.4141
Pulmonary artery mean pressure - mmHg	31.8 ± 10.2 (497)	31.9 ± 9.6 (499)	0.6693
Heart rate - bpm	78.8 ± 11.7 (497)	79.4 ± 11.9 (499)	0.7893
Laboratory Analyses			
Serum creatinine level - µmol/L	128.5 ± 44.5 (495)	133.5 ± 48.5 (495)	0.1548
Estimated glomerular filtration rate - ml/min/1.73m^2	54.3 ± 21.3 (495)	52.8 ± 20.8 (494)	0.2469
B-type natriuretic peptide level - pg/mL	520.7 ± 689.2 (261)	552.4 ± 954.0 (256)	0.8499
N-terminal pro-B-type natriuretic peptide level - pg/mL	2460 ± 3707 (219)	2183 ± 2803 (225)	0.5287
Treatment History			
Previous cardiac resynchronization therapy	28.6% (142/497)	32.4% (163/503)	0.1926
Previous implantation of defibrillator	42.9% (213/497)	40.8% (205/503)	0.5217
Guideline-Directed Medical Therapy			
ACE-Inhibitor or ARB or ARNi	64.2% (319/497)	63.6% (320/503)	0.8953
ARNi	29.2% (145/497)	27.6% (139/503)	0.6236
Beta Blocker	89.3% (444/497)	87.9% (442/503)	0.4873
Mineralocorticoid Receptor Antagonist	47.7% (237/497)	42.9% (216/503)	0.1440
Diuretic	95.4% (474/497)	95.0% (478/503)	0.8827
Hydralazine	16.3% (81/497)	15.9% (80/503)	0.9315
Nitrate	19.9% (99/497)	20.5% (103/503)	0.8749
SGLT2 Inhibitor	1.3% (2/152)	1.4% (2/140)	1.0000
Enrollment Type			
Heart failure hospitalization in year prior only	34.2% (170/497)	38.0% (191/502)	0.2114
Elevated natriuretic peptide level in 30 day prior only	46.3% (230/497)	42.2% (212/502)	0.2032
Heart failure hospitalization in year prior and elevated natriuretic peptide level in 30 day prior	19.5% (97/497)	19.7% (99/502)	0.9367
KCCQ-12 at Baseline – Overall Summary Score	54.9 ± 24.3 (494)	54.9 ± 23.8 (497)	0.8876
6MHW at Baseline – m	235.2 ± 120.2 (474)	229.6 ± 123.0 (482)	0.4459

Continuous Variables: Mean ± SD (n); Categorical Variables: Percent (n/N)
[1]Continuous variables compared using Wilcoxon Rank Sum test, and categorical variables compared using Fisher's exact test.

D. Safety and Effectiveness Results

1. Effectiveness Results

Primary Endpoint

The primary endpoint analysis was based on all randomized subjects. At 12 months, there were 253 primary endpoint events in the Treatment group compared with 289 events in the Control group. The difference between the groups represented a non-significant 12% relative risk reduction in the primary endpoint events (0.563 vs. 0.640 events per patient-year; HR 0.88, 95% CI 0.74-1.05, p=0.1624). Since the 97.5% upper confidence bound of the hazard ratio was not

less than 1, the primary endpoint was not met.

Table 3 presents the primary endpoint analysis and the components. There were 185 heart failure hospitalizations in the treatment group and 225 in the control group (0.410 vs. 0.497 events per patient; HR 0.83, 95% CI 0.68-1.01). The rates of urgent heart failure ED/outpatient visits or mortality were similar between the two groups.

The timing of the pivotal study overlapped with the COVID-19 pandemic. The effects of the pandemic on the study outcomes are further assessed in the sensitivity analysis section below.

Table 3. Primary Endpoint Analysis and Components

Endpoint[1]	Treatment (N=497) Events (Rate[2])	Control (N=503) Events (Rate[2])	Hazard Ratio (95% CI) p-value[3]
HF Hospitalization + ED/OP + Death (Primary Endpoint)	253 (0.563)	289 (0.640)	0.88 (0.74, 1.05), p=0.1624
HF Hospitalization + ED/OP (Secondary Endpoint)	213 (0.474)	252 (0.557)	0.85 (0.70, 1.03)
HF Hospitalization	185 (0.410)	225 (0.497)	0.83 (0.68, 1.01)
HF Emergency Department/Hospital Outpatient Visit (ED/OP)	28 (0.065)	27 (0.063)	1.04 (0.61, 1.77)
Death	40 (0.094)	37 (0.086)	1.09 (0.70, 1.70)

[1]Endpoints include CEC adjudicated Heart Failure (HF) Hospitalizations or HF Emergency Department/Hospital Outpatient Visits (ED/OP) with an admission date after the date of implant hospitalization discharge through 395 days after the date of implant. All Cause Deaths are included from implant date to 395 days after implant date.
[2]Event Rate is an annualized rate estimated from the Andersen-Gill model.
[3]Hazard Ratio, 95% Confidence Interval, and p-value estimated from the Andersen-Gill model with robust sandwich variance estimates.

COVID-19 Impact Sensitivity Analysis

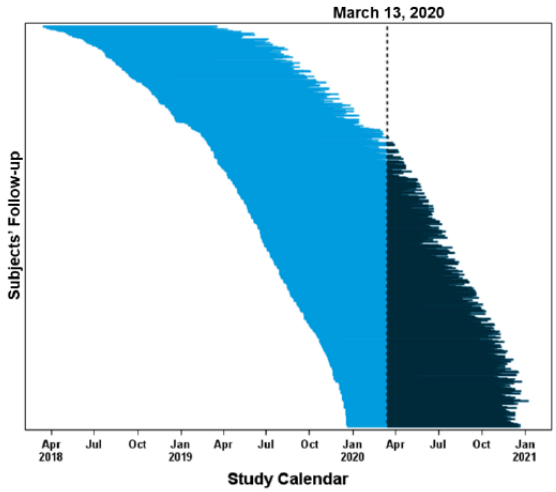
COVID-19 Sensitivity Analysis for Interaction

The COVID-19 pandemic occurred while the pivotal study was still ongoing. Across North America, hospitals saw notable reduction in heart failure hospital admissions during COVID-19 lockdowns. Using the national emergency declaration date (March 13, 2020) in the United States as the onset date, a total of 71.7% of follow-up had been completed prior to COVID-19. The median follow-up prior to COVID-19 was 8.4 months.

The applicant added a COVID-19 impact sensitivity analysis (dated July 7, 2020) to the statistical analysis plan prior to data unblinding. The sensitivity analysis would descriptively compare the primary endpoint event rates observed during subject follow-up occurring prior to the start of the COVID-19 pandemic to rates

observed during subject follow-up occurring after the start of the pandemic to evaluate impact of COVID-19, as shown in Figure 6.

Figure 6. Follow-up Based Sensitivity Analysis



The sensitivity analysis demonstrated a qualitative interaction with a significant p-value of p=0.1129 (<p=0.15, pre-specified interaction p-value threshold), suggesting an impact of COVID-19 on the treatment effect observed in the Randomization Arm of the GUIDE-HF trial (Table 4). The hazard ratio for the primary endpoint events reversed from 0.81 prior to COVID-19 to 1.11 during COVID-19.

Table 4. Primary Endpoint – Follow-Up Based COVID-19 Sensitivity Analysis

Endpoint[1]	Treatment (N=497) Events	Control (N=503) Events	Forest Plot	Hazard Ratio (95% CI)[2]
Heart Failure Hospitalization + ED/OP + Death (Primary Endpoint)				**Interaction p-value[3]** p=0.1129
Prior to COVID-19[4]	177	224		0.81 (0.66, 1.00)
During COVID-19[4]	76	65		1.11 (0.80, 1.55)
			0.5 0.75 1 1.25 1.5 1.75	

[1]Endpoints include CEC adjudicated Heart Failure (HF) Hospitalizations or HF Emergency Department/Hospital Outpatient Visits (ED/OP) with an admission date after the date of implant hospitalization discharge through 395 days after the date of implant. All Cause Deaths are included from implant date to 395 days after implant date.
[2]Contrast Comparison Hazard Ratio and 95% Confidence Interval estimated from the Andersen-Gill model with robust sandwich estimates.
[3]Interaction p-value is a joint test on the interaction term of treatment group by COVID analysis time period.
[4]Primary Endpoint events are analyzed through March 13, 2020 for Prior to COVID-19 and analyzed after March 13, 2020 for During COVID-19.

Since the COVID-19 sensitivity analysis suggested an effect of COVID-19 on the primary endpoint, the pre-pandemic data were further explored.

Pre-COVID-19 Analysis

Pre-pandemic Primary Endpoint Events

Prior to COVID-19, there were a total of 177 primary endpoint events in the Treatment group compared with 224 events in the Control group (0.595 events vs. 0.730 events per patient, respectively). An HR of 0.81 (95% CI 0.66-1.00) for the primary endpoint, largely driven by a 27% reduction in risk for HFH, was observed.

The results of the analysis including data prior to COVID-19 only are shown in Table 5 below:

Table 5. Primary Endpoint and Components – Including Data Prior to COVID-19 Only

Endpoint[1]	Treatment (N=497) Events (Rate[2])	Control (N=503) Events (Rate[2])	Hazard Ratio (95% CI)[3]
HF Hospitalization + ED/OP + Death (Primary Endpoint)	177 (0.595)	224 (0.730)	0.81 (0.66, 1.00)
HF Hospitalization + ED/OP (Secondary Endpoint)	147 (0.502)	199 (0.660)	0.76 (0.61, 0.95)
HF Hospitalization	124 (0.426)	176 (0.587)	0.73 (0.57, 0.92)
HF Emergency Department/Hospital Outpatient Visit (ED/OP)	23 (0.077)	23 (0.076)	1.02 (0.57, 1.82)
Death	30 (0.103)	25 (0.083)	1.24 (0.73, 2.10)

[1]Endpoints include CEC adjudicated Heart Failure (HF) Hospitalizations or HF Emergency Department/Hospital Outpatient Visits (ED/OP) with an admission date after the date of implant hospitalization discharge through 395 days after the date of implant. All Cause Deaths are included from implant date to 395 days after implant date. Primary Endpoint events are analyzed through March 13, 2020.
[2]Event Rate is an annualized rate estimated from the Andersen-Gill model.
[3]Hazard Ratio and 95% Confidence Interval estimated from the Andersen-Gill model with robust sandwich variance estimates.
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Quality of Life Assessment and Functional Assessment (6MHW)

Health status changes over time were assessed by EuroQol 5-Dimension, 5-Level (EQ-5D-5L) Questionnaire and Kansas City Cardiomyopathy Questionnaire (KCCQ-12) at baseline, 6, and 12 months. While both Treatment and Control groups gained improvement at 6 months, there were no significant differences between the groups (Table 6).

The functional assessment of 6MHW distance did not show a significant improvement either within or between groups over the follow-up period.

Table 6. KCCQ-12, EQ-5D-5L, and 6MHW

Component/Analysis	6 Month Paired Change from Baseline			12 Month Paired Change from Baseline		
	Treatment Mean ± SD (n)	**Control** Mean ± SD (n)	Between Group p-value	**Treatment** Mean ± SD (n)	**Control** Mean ± SD (n)	Between Group p-value
KCCQ-12 Overall Summary Score	7.44 ± 20.68 (449)	6.14 ± 24.72 (440)	0.3545[1]	5.20 ± 21.35 (421)	4.12 ± 22.50 (408)	0.4783[1]
EQ-5D-5L Visual Analogue Scale	3.09 ± 19.40 (449)	3.20 ± 21.69 (441)	0.9363[1]	0.94 ± 20,17 (421)	2.90 ± 20.71 (409)	0.1658[1]
6MHW Test Distance	0.01 ± 87.78 (332)	2.29 ± 93.69 (342)	0.7439[1]	-12.83 ± 100.08 (288)	-6.46 ± 106.57 (291)	0.4586[1]

[1]Student t-test comparing Treatment vs. Control change from baseline at 6 months and 12 months

PA Pressures

A greater reduction in PA mean pressure over time was observed in the Treatment group compared to Control (-2.4 ± 5.2 mmHg vs. -1.7 ± 5.0; Figure 7). A greater reduction in Treatment group PA mean pressure was also observed when limited to data prior to COVID-19 (-2.1 ± 4.8 mmHg vs. -1.4 ± 4.8; Figure 8).

Figure 7. Average PA Mean Pressure Over Time

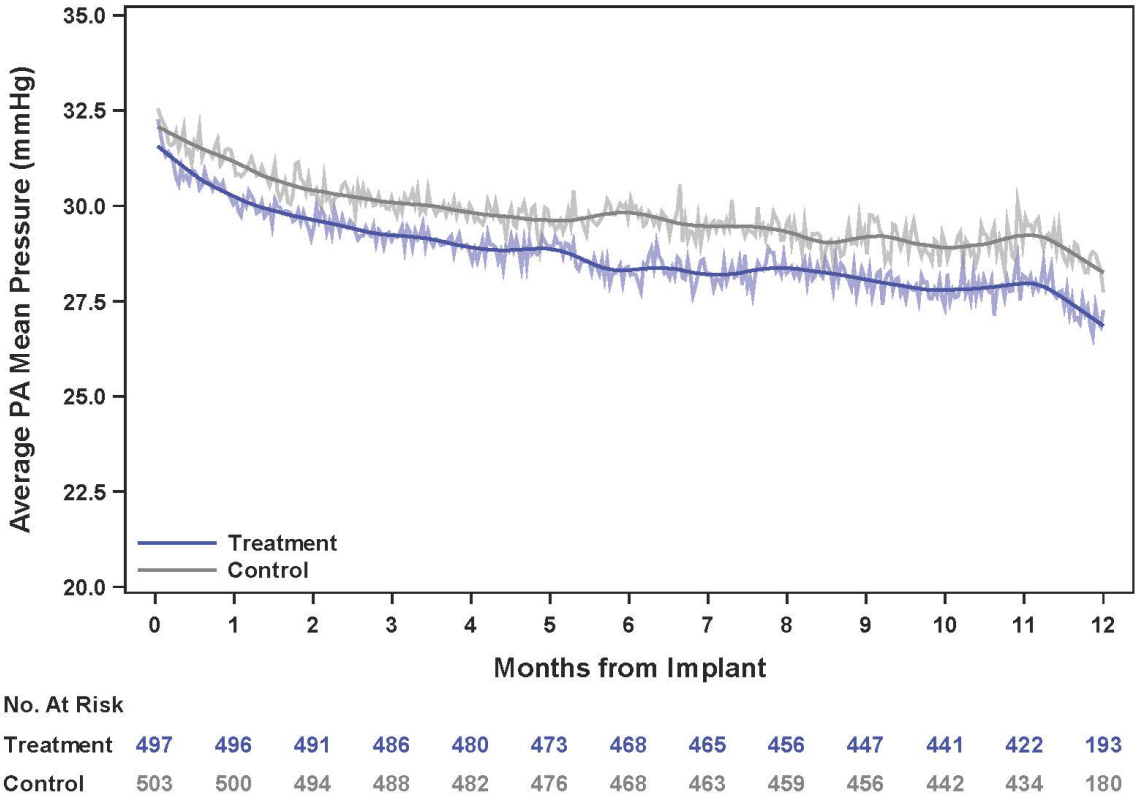
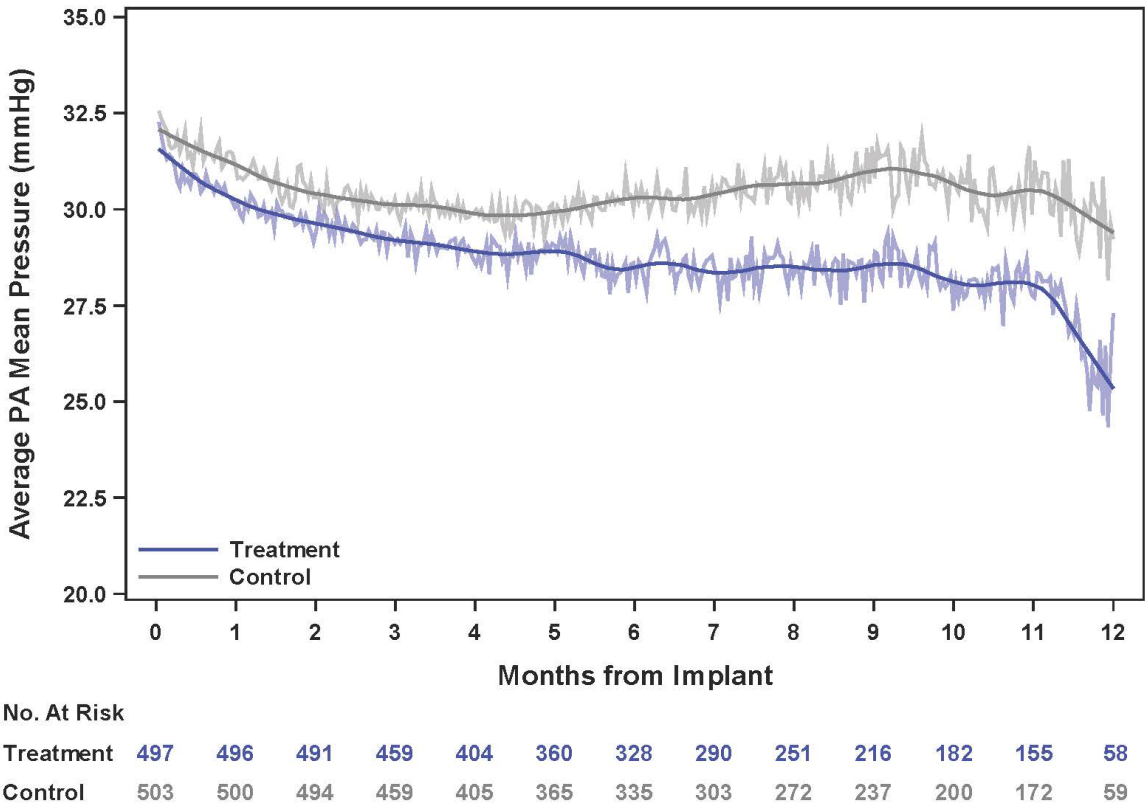


Figure 8. Average PA Mean Pressure Over Time – Data Prior to COVID-19 Only



No. At Risk													
Treatment	497	496	491	459	404	360	328	290	251	216	182	155	58
Control	503	500	494	459	405	365	335	303	272	237	200	172	59

2. Safety Results

Freedom from Device or System Related Complications (DSRC)

A total of 8 DSRC events occurred in 8 subjects in the safety population. The observed rate of freedom from Device or System Related Complications was 99.2% (1014/1022). None of the 8 DSRCs resulted in death or explant of the device, and most were vascular injury events due to vascular access or device implant. Table 7 presents a summary of DSRCs.

Table 7. Summary of DSRCs as Adjudicated by the CEC (Safety Population)

Cohort System Organ Class Preferred Term	Number of DSRCs	Proportion of Subjects with DSRCs	DSRC Criteria Met		
			Treated with Invasive Means	Resulted in Death	Resulted in Device Explant
Safety Population (N=1022)					
General Disorders and Administration Site Conditions	**5**	**0.49% (5/1022)**	**5**	**0**	**0**
Catheter Site Hematoma	1	0.10% (1/1022)	1	0	0
Catheter Site Hemorrhage	2	0.20% (2/1022)	2	0	0
Device Dislocation	1	0.10% (1/1022)	1	0	0
Device Malfunction	1	0.10% (1/1022)	1	0	0
Injury, Poisoning and Procedural Complications	**3**	**0.29% (3/1022)**	**3**	**0**	**0**
Arterial Injury	2	0.20% (2/1022)	2	0	0
Vascular Pseudoaneurysm	1	0.10% (1/1022)	1	0	0
Total	**8**	**0.78% (8/1022)**	**8**	**0**	**0**

Hospitalizations

Table 8 summarizes the all-cause hospitalizations reported during the 12-month follow-up for all randomized subjects. Treatment group experienced a lower all-cause hospitalizations rate comparing to the Control group (468 vs. 493) though similar proportion of subjects in each group had at least one hospitalization during the study.

Table 8. Summary of Hospitalizations as Adjudicated by the CEC (Endpoint Analysis Population)

Adjudicated Cause	Treatment (N=497) Count [Rate[1]]	Treatment (N=497) Percent of Subjects with Event	Control (N=503) Count [Rate[1]]	Control (N=503) Percent of Subjects with Event
Worsening heart failure	**233 [50.3]**	**27.4% (136/497)**	**269 [57.7]**	**30.4% (153/503)**
HF Hospitalization	185 [39.9]	24.1% (120/497)	225 [48.2]	27.6% (139/503)
Urgent HF Visit	28 [6.04]	4.4% (22/497)	27 [5.79]	5.0% (25/503)
Not a Protocol Defined HF Admission	20 [4.32]	3.4% (17/497)	17 [3.65]	3.0% (15/503)
Other cardiovascular	**200 [43.2]**	**27.4% (136/497)**	**186 [39.9]**	**25.0% (126/503)**
CABG	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Myocardial Infarction or Other Forms of Ischemic Heart Disease	26 [5.61]	4.0% (20/497)	46 [9.86]	7.6% (38/503)
Product Issue[2]	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Thrombosis or Thromboembolism	12 [2.59]	2.0% (10/497)	6 [1.29]	1.2% (6/503)
Valve Surgery	5 [1.08]	0.8% (4/497)	6 [1.29]	1.2% (6/503)
Ventricular or Atrial Arrhythmia	57 [12.3]	9.1% (45/497)	55 [11.8]	8.5% (43/503)
Other	99 [21.4]	14.7% (73/497)	72 [15.4]	11.9% (60/503)
Non-cardiovascular	**35 [7.55]**	**6.8% (34/497)**	**37 [7.93]**	**6.4% (32/503)**
Total	**468 [101.0]**	**47.1% (234/497)**	**492 [105.5]**	**46.5% (234/503)**

[1]Rate is number of events per 100 subject years.

[2]Hospitalization due to events related to the device.

Mortality

A total of 77 subjects died in the study. There were 40 (0.094) all-cause deaths in the Treatment group and 37 (0.086) all-cause deaths in the Control group. Table 9 presents the causes of deaths between the two groups per CEC adjudication.

Table 9. Summary of Deaths as Adjudicated by the CEC (Endpoint Analysis Population)

Adjudicated Cause	Treatment (N=497)	Control (N=503)
Cardiovascular	**6.0% (30/497)**	**4.8% (24/503)**
Cardiovascular procedure	0.2% (1/497)	0.0% (0/503)
Heart failure	3.4% (17/497)	3.0% (15/503)
Sudden cardiac death	2.2% (11/497)	1.8% (9/503)
Other	0.2% (1/497)	0.0% (0/503)
Non-cardiovascular	**1.6% (8/497)**	**2.6% (13/503)**
Gastrointestinal	0.0% (0/497)	0.2% (1/503)
Hemorrhage	0.0% (0/497)	0.2% (1/503)
Infection	0.6% (3/497)	0.6% (3/503)
Inflammatory, Immune (including autoimmune)	0.0% (0/497)	0.2% (1/503)
Neurological	0.2% (1/497)	0.2% (1/503)
Pulmonary	0.2% (1/497)	0.4% (2/503)
Renal	0.4% (2/497)	0.4% (2/503)
Other non-cardiovascular	0.2% (1/497)	0.4% (2/503)
Undetermined cause of death	**0.4% (2/497)**	**0.0% (0/503)**
Total	**8.0% (40/497)**	**7.4% (37/503)**

There were no device-related deaths.

Two subjects died within 30 days after the procedure. A patient with ischemic cardiomyopathy, atrial fibrillation and a history of valvular heart disease status post TAVR developed abdominal pain post-operatively. The patient was found to have ischemic bowel and died on post-operative day 2. The death was adjudicated as procedure-related but not device-related. Another patient died of sudden cardiac arrest on day 29 after the procedure. CEC adjudicated the death as not device- or procedure-related.

Adverse Events

Table 10 presents a summary of adverse events as reported by investigators. There were no unanticipated adverse device effects. Tables 11 and 12 present the serious and non-serious adverse device effects reported in the pivotal study.

Table 10. Summary of Adverse Events (As Reported by Investigator)

Adverse Event Class	Treatment (N=497) Events [Rate[1]]	Treatment (N=497) Percent of Subjects with Event	Control (N=503) Events [Rate[1]]	Control (N=503) Percent of Subjects with Event
SAE	729 [157.3]	56.7% (282/497)	799 [171.3]	53.3% (268/503)
ADE	16 [3.45]	3.0% (15/497)	20 [4.29]	4.0% (20/503)
SADE	9 [1.94]	1.8% (9/497)	15 [3.22]	2.4% (12/503)
UADE	0 [0.00]	0.0% (0/497)	0 [0.00]	0.0% (0/503)

[1]Rate is number of events per 100 subject years.

Table 11. Summary of Serious Adverse Device Effects (As Reported by Investigator)

System Organ Class Preferred Term	Treatment (N=497) Events [Rate[1]]	Treatment (N=497) Percent of Subjects with Event	Control (N=503) Events [Rate[1]]	Control (N=503) Percent of Subjects with Event
Overall Follow-Up				
Cardiac Disorders	**2 [0.43]**	**0.4% (2/497)**	**0 [0.00]**	**0.0% (0/503)**
Arrhythmia	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Cardiac Failure Congestive	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
General Disorders and Administration Site Conditions[2]	**4 [0.86]**	**0.8% (4/497)**	**4 [0.86]**	**0.8% (4/503)**
Catheter Site Hematoma	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Catheter Site Hemorrhage	4 [0.86]	0.8% (4/497)	1 [0.21]	0.2% (1/503)
Device Deployment Issue[3]	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Device Dislocation[4]	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Injury, Poisoning and Procedural Complications	**1 [0.22]**	**0.2% (1/497)**	**2 [0.43]**	**0.4% (2/503)**
Arterial Injury	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Vascular Pseudoaneurysm	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Respiratory, Thoracic and Mediastinal Disorders	**0 [0.00]**	**0.0% (0/497)**	**6 [1.29]**	**1.0% (5/503)**
Hemoptysis	0 [0.00]	0.0% (0/497)	4 [0.86]	0.6% (3/503)
Pulmonary Embolism	0 [0.00]	0.0% (0/497)	2 [0.43]	0.4% (2/503)
Vascular Disorders	**2 [0.43]**	**0.4% (2/497)**	**3 [0.64]**	**0.6% (3/503)**
Embolism	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Hematoma	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
Thrombosis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Total	**9 [1.94]**	**1.8% (9/497)**	**15 [3.22]**	**2.4% (12/503)**

[1]Rate is number of events per 100 subject years.
[2]Administration Site Conditions refers to events associated with site at which the device is administered
[3]Device did not completely detach from delivery catheter upon initial deployment, but was ultimately deployed and confirmed to be working successfully.
[4]Partial dislodgment of a left ventricular pacemaker lead during the CardioMEMS device implantation procedure, requiring subsequent lead revision. All SADEs occurred in NYHA Class II/III subjects prior to COVID-19.

Table 12. Summary of Adverse Device Effects (As Reported by Investigator)

	Treatment (N=497)	Control (N=503)

System Organ Class Preferred Term	Events [Rate[1]]	Percent of Subjects with Event	Events [Rate[1]]	Percent of Subjects with Event
Cardiac Disorders	**0 [0.00]**	**0.0% (0/497)**	**2 [0.43]**	**0.4% (2/503)**
Arrhythmia	0 [0.00]	0.0% (0/497)	2 [0.43]	0.4% (2/503)
General Disorders and Administration Site Conditions	**9 [1.94]**	**1.8% (9/497)**	**18 [3.86]**	**3.6% (18/503)**
Catheter Site Hematoma	2 [0.43]	0.4% (2/497)	3 [0.64]	0.6% (3/503)
Catheter Site Hemorrhage	4 [0.86]	0.8% (4/497)	6 [1.29]	1.2% (6/503)
Device Deployment Issue	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Device Dislocation	0 [0.00]	0.0% (0/497)	3 [0.64]	0.6% (3/503)
Device Information Output Issue	2 [0.43]	0.4% (2/497)	2 [0.43]	0.4% (2/503)
Device Malfunction	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Pyrexia	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Vessel Puncture Site Pain	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Injury, Poisoning and Procedural Complications	**2 [0.43]**	**0.4% (2/497)**	**0 [0.00]**	**0.0% (0/503)**
Arterial Injury	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Laceration	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Nervous System Disorders	**1 [0.22]**	**0.2% (1/497)**	**0 [0.00]**	**0.0% (0/503)**
Presyncope	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Respiratory, Thoracic and Mediastinal Disorders	**3 [0.65]**	**0.6% (3/497)**	**0 [0.00]**	**0.0% (0/503)**
Hemoptysis	3 [0.65]	0.6% (3/497)	0 [0.00]	0.0% (0/503)
Vascular Disorders	**1 [0.22]**	**0.2% (1/497)**	**0 [0.00]**	**0.0% (0/503)**
Hypotension	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Total	**16 [3.45]**	**3.0% (15/497)**	**20 [4.29]**	**4.0% (20/503)**

[1]Rate is number of events per 100 subject years.
All ADEs occurred in NYHA Class II/III subjects prior to COVID-19.

Serious Adverse Events

A serious adverse event (SAE) was defined as an adverse event not related to the use of the device but meeting seriousness criteria (requiring hospitalization or invasive intervention or resulting in a life-threatening illness or injury). A summary of non- device-related investigator-reported SAEs is provided in Table 13 below.

Table 13. Summary of Serious Adverse Events (As Reported by Investigator)

	Treatment (N=497)		Control (N=503)	
System Organ Class Preferred Term	**Events [Rate[1]]**	**Percent of Subjects with Event**	**Events [Rate[1]]**	**Percent of Subjects with Event**
Blood and Lymphatic System Disorders	**11 [2.37]**	**1.6% (8/497)**	**8 [1.72]**	**1.4% (7/503)**
Anemia	9 [1.94]	1.2% (6/497)	8 [1.72]	1.4% (7/503)
Thrombocytopenia	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Cardiac Disorders	**302 [65.2]**	**32.6% (162/497)**	**389 [83.4]**	**38.8% (195/503)**
Acute Myocardial Infarction	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Angina Pectoris	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)

System Organ Class	Treatment (N=497) Events [Rate[1]]	Treatment (N=497) Percent of	Control (N=503) Events [Rate[1]]	Control (N=503) Percent of
Angina Unstable	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Aortic Valve Disease	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Arrhythmia	53 [11.4]	9.5% (47/497)	54 [11.6]	9.1% (46/503)
Atrioventricular Block Complete	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Cardiac Aneurysm	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Cardiac Arrest	3 [0.65]	0.6% (3/497)	4 [0.86]	0.8% (4/503)
Cardiac Failure Congestive	216 [46.6]	26.2% (130/497)	276 [59.2]	30.8% (155/503)
Cardiac Perforation	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Cardiac Valve Disease	1 [0.22]	0.2% (1/497)	4 [0.86]	0.6% (3/503)
Cardiogenic Shock	8 [1.73]	1.6% (8/497)	6 [1.29]	1.0% (5/503)
Cardiomyopathy	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Coronary Artery Disease	1 [0.22]	0.2% (1/497)	9 [1.93]	1.6% (8/503)
Intracardiac Thrombus	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Ischemic Cardiomyopathy	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Mitral Valve Disease	1 [0.22]	0.2% (1/497)	3 [0.64]	0.4% (2/503)
Mitral Valve Incompetence	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Myocardial Infarction	11 [2.37]	2.0% (10/497)	16 [3.43]	3.2% (16/503)
Pericardial Effusion	1 [0.22]	0.2% (1/497)	3 [0.64]	0.6% (3/503)
Pericarditis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Prinzmetal Angina	0 [0.00]	0.0% (0/497)	2 [0.43]	0.4% (2/503)
Restrictive Cardiomyopathy	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Tachycardia	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
Ear and Labyrinth Disorders	**2 [0.43]**	**0.4% (2/497)**	**0 [0.00]**	**0.0% (0/503)**
Vertigo	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Vertigo Positional	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Endocrine Disorders	**2 [0.43]**	**0.4% (2/497)**	**0 [0.00]**	**0.0% (0/503)**
Hypothyroidism	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Inappropriate Antidiuretic Hormone Secretion	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Gastrointestinal Disorders	**29 [6.26]**	**4.8% (24/497)**	**33 [7.08]**	**5.0% (25/503)**
Abdominal Pain	0 [0.00]	0.0% (0/497)	2 [0.43]	0.4% (2/503)
Colitis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Colitis Ischemic	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Colonic Stenosis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Constipation	2 [0.43]	0.4% (2/497)	1 [0.21]	0.2% (1/503)
Diarrhea	2 [0.43]	0.4% (2/497)	1 [0.21]	0.2% (1/503)
Duodenal Ulcer	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Dysphagia	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Gastritis	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Gastrointestinal Hemorrhage	10 [2.16]	1.8% (9/497)	20 [4.29]	3.2% (16/503)
Gastrointestinal Necrosis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Gastroesophageal Reflux Disease	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Hemorrhoidal Hemorrhage	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Ileus	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Impaired Gastric Emptying	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Intestinal Ischemia	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)

System Organ Class	Treatment (N=497) Events [Rate[1]]	Percent of	Control (N=503) Events [Rate[1]]	Percent of
Nausea	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Pancreatic Mass	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Pancreatitis	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Pancreatitis Acute	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Proctitis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Small Intestinal Obstruction	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
Spigelian Hernia	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Vomiting	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
General Disorders and Administration Site Conditions[1]	**49 [10.6]**	**8.2% (41/497)**	**34 [7.29]**	**6.2% (31/503)**
Accidental Death[2]	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Asthenia	4 [0.86]	0.8% (4/497)	3 [0.64]	0.6% (3/503)
Catheter Site Hematoma	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Chest Pain	32 [6.90]	5.4% (27/497)	25 [5.36]	4.6% (23/503)
Death[3]	3 [0.65]	0.6% (3/497)	0 [0.00]	0.0% (0/503)
Device Dislocation[4]	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Device Electrical Impedance Issue[5]	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Device Malfunction[6]	0 [0.00]	0.0% (0/497)	3 [0.64]	0.6% (3/503)
Fatigue	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Generalized Edema	2 [0.43]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Hypothermia	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Implant Site Hemorrhage	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Multi-Organ Failure	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Polyp	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Sudden Cardiac Death[7]	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Hepatobiliary Disorders	**4 [0.86]**	**0.8% (4/497)**	**4 [0.86]**	**0.8% (4/503)**
Cholangitis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Cholelithiasis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Hepatic Cirrhosis	2 [0.43]	0.4% (2/497)	2 [0.43]	0.4% (2/503)
Hepatic Function Abnormal	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Ischemic Hepatitis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Immune System Disorders	**0 [0.00]**	**0.0% (0/497)**	**2 [0.43]**	**0.4% (2/503)**
Drug Hypersensitivity	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Heart Transplant Rejection	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Infections and Infestations	**99 [21.4]**	**15.3% (76/497)**	**113 [24.2]**	**16.9% (85/503)**
Abscess	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Anal Abscess	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Bronchitis	2 [0.43]	0.4% (2/497)	7 [1.50]	1.4% (7/503)
Cellulitis	6 [1.29]	1.0% (5/497)	8 [1.72]	1.4% (7/503)

[1] Administration Site Conditions refers to events associated with site at which the device is administered.
[2] Traumatic death in an accident.
[3] Unknown event leading to death.
[4] Hip prosthesis dislocation, unrelated to study device.
[5] Broken pacemaker lead, unrelated to study device.
[6] Cardiac pacemaker or ICD malfunction, unrelated to study device.
[7] Sudden cardiac death due to ischemic heart disease.

System Organ Class	Treatment (N=497) Events [Rate[1]]	Treatment (N=497) Percent of	Control (N=503) Events [Rate[1]]	Control (N=503) Percent of
Central Nervous System Abscess	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Clostridial Infection	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Corona Virus Infection	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
Cystitis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Endocarditis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Gastroenteritis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Gastroenteritis Viral	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Gastrointestinal Infection	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Herpes Zoster	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Infection	29 [6.26]	5.4% (27/497)	39 [8.36]	6.8% (34/503)
Influenza	3 [0.65]	0.6% (3/497)	1 [0.21]	0.2% (1/503)
Intervertebral Discitis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Mycotic Aneurysm	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Pneumonia	27 [5.83]	4.8% (24/497)	32 [6.86]	5.8% (29/503)
Sepsis	18 [3.88]	3.4% (17/497)	10 [2.14]	2.0% (10/503)
Septic Shock	0 [0.00]	0.0% (0/497)	4 [0.86]	0.8% (4/503)
Upper Respiratory Tract Infection	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
Urinary Tract Infection	3 [0.65]	0.6% (3/497)	4 [0.86]	0.8% (4/503)
Wound Infection	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Injury, Poisoning and Procedural Complications	**15 [3.24]**	**2.8% (14/497)**	**16 [3.43]**	**3.0% (15/503)**
Cervical Vertebral Fracture	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Fall	4 [0.86]	0.8% (4/497)	6 [1.29]	1.0% (5/503)
Femur Fracture	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Hip Fracture	2 [0.43]	0.4% (2/497)	3 [0.64]	0.6% (3/503)
Iliotibial Band Syndrome	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Joint Injury	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Laceration	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Multiple Fractures	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Pelvic Fracture	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Road Traffic Accident[8]	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Spinal Compression Fracture	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Spinal Fracture	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Subdural Hematoma	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Vascular Pseudoaneurysm	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Investigations	**21 [4.53]**	**3.8% (19/497)**	**21 [4.50]**	**3.0% (15/503)**
Anticoagulation Drug Level Below Therapeutic	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Blood Creatinine Increased	18 [3.88]	3.4% (17/497)	17 [3.65]	2.6% (13/503)
International Normalized Ratio Decreased	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
International Normalized Ratio Increased	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Left Ventricular End-Diastolic Pressure Increased	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)

[8] Multiple injuries and surgical procedures resulting from a motor vehicle accident.

System Organ Class	Treatment (N=497) Events [Rate[1]]	Treatment (N=497) Percent of	Control (N=503) Events [Rate[1]]	Control (N=503) Percent of
Transaminases Increased	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Troponin Increased	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Metabolism and Nutrition Disorders	**25 [5.39]**	**4.8% (24/497)**	**24 [5.15]**	**4.0% (20/503)**
Dehydration	8 [1.73]	1.6% (8/497)	2 [0.43]	0.4% (2/503)
Diabetes Mellitus	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Diabetic Ketoacidosis	0 [0.00]	0.0% (0/497)	2 [0.43]	0.4% (2/503)
Fluid Overload	2 [0.43]	0.4% (2/497)	2 [0.43]	0.2% (1/503)
Gout	2 [0.43]	0.4% (2/497)	2 [0.43]	0.4% (2/503)
Hyperglycemia	5 [1.08]	1.0% (5/497)	5 [1.07]	0.8% (4/503)
Hyperkalemia	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Hypoglycemia	2 [0.43]	0.4% (2/497)	4 [0.86]	0.8% (4/503)
Hypokalemia	1 [0.22]	0.2% (1/497)	3 [0.64]	0.6% (3/503)
Hypovolemia	1 [0.22]	0.2% (1/497)	3 [0.64]	0.6% (3/503)
Lactic Acidosis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Type 2 Diabetes Mellitus	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Musculoskeletal and Connective Tissue Disorders	**14 [3.02]**	**2.4% (12/497)**	**4 [0.86]**	**0.8% (4/503)**
Arthralgia	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Back Pain	5 [1.08]	0.6% (3/497)	0 [0.00]	0.0% (0/503)
Compartment Syndrome	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Fibromyalgia	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Muscular Weakness	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Myopathy	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Osteoarthritis	2 [0.43]	0.4% (2/497)	1 [0.21]	0.2% (1/503)
Rhabdomyolysis	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Rheumatoid Arthritis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Spinal Osteoarthritis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**2 [0.43]**	**0.4% (2/497)**	**2 [0.43]**	**0.4% (2/503)**
Colon Cancer	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Lung Neoplasm	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Esophageal Adenocarcinoma	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Squamous Cell Carcinoma	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Nervous System Disorders	**42 [9.06]**	**7.4% (37/497)**	**28 [6.00]**	**4.8% (24/503)**
Carotid Artery Stenosis	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Cerebrovascular Accident	12 [2.59]	2.2% (11/497)	6 [1.29]	1.2% (6/503)
Cerebrovascular Disorder	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Cervicogenic Headache	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
CNS Ventriculitis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Complicated Migraine	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Convulsion	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Dizziness	4 [0.86]	0.8% (4/497)	4 [0.86]	0.8% (4/503)
Encephalopathy	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Hemorrhage Intracranial	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Headache	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)

System Organ Class	Treatment (N=497) Events [Rate[1]]	Treatment (N=497) Percent of	Control (N=503) Events [Rate[1]]	Control (N=503) Percent of
Hepatic Encephalopathy	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Hypoesthesia	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Metabolic Encephalopathy	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Myoclonus	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Partial Seizures	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Presyncope	3 [0.65]	0.6% (3/497)	0 [0.00]	0.0% (0/503)
Sciatica	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Subarachnoid Hemorrhage	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Syncope	12 [2.59]	2.4% (12/497)	8 [1.72]	1.6% (8/503)
Transient Ischemic Attack	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Vertebral Artery Stenosis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Psychiatric Disorders	**3 [0.65]**	**0.6% (3/497)**	**6 [1.29]**	**1.0% (5/503)**
Depression	0 [0.00]	0.0% (0/497)	3 [0.64]	0.4% (2/503)
Mental Disorder	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Mental Status Changes	2 [0.43]	0.4% (2/497)	3 [0.64]	0.6% (3/503)
Renal and Urinary Disorders	**29 [6.26]**	**4.8% (24/497)**	**41 [8.79]**	**7.6% (38/503)**
Hematuria	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Nephrolithiasis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Obstructive Uropathy	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Renal Failure	3 [0.65]	0.6% (3/497)	1 [0.21]	0.2% (1/503)
Renal Failure Acute	21 [4.53]	3.6% (18/497)	29 [6.22]	5.6% (28/503)
Renal Failure Chronic	2 [0.43]	0.4% (2/497)	6 [1.29]	1.0% (5/503)
Urinary Retention	3 [0.65]	0.6% (3/497)	2 [0.43]	0.4% (2/503)
Reproductive System and Breast Disorders	**1 [0.22]**	**0.2% (1/497)**	**1 [0.21]**	**0.2% (1/503)**
Benign Prostatic Hyperplasia	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Vaginal Hemorrhage	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Respiratory, Thoracic and Mediastinal Disorders	**42 [9.06]**	**6.8% (34/497)**	**52 [11.2]**	**7.6% (38/503)**
Acute Respiratory Failure	3 [0.65]	0.6% (3/497)	8 [1.72]	1.6% (8/503)
Asthma	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Chronic Obstructive Pulmonary Disease	13 [2.80]	1.8% (9/497)	24 [5.15]	2.8% (14/503)
Chronic Respiratory Disease	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Cough	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Dyspnea	7 [1.51]	1.4% (7/497)	8 [1.72]	1.6% (8/503)
Epistaxis	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Hemoptysis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Hypoxia	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Pleural Effusion	5 [1.08]	0.8% (4/497)	4 [0.86]	0.8% (4/503)
Pneumothorax	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Pulmonary Alveolar Hemorrhage	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Pulmonary Embolism	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Pulmonary Hypertension	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Respiratory Failure	4 [0.86]	0.8% (4/497)	3 [0.64]	0.6% (3/503)
Sleep Apnea Syndrome	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)

System Organ Class	Treatment (N=497) Events [Rate[1]]	Treatment (N=497) Percent of	Control (N=503) Events [Rate[1]]	Control (N=503) Percent of
Skin and Subcutaneous Tissue Disorders	**2 [0.43]**	**0.4% (2/497)**	**0 [0.00]**	**0.0% (0/503)**
Angioedema	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Hyperhidrosis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Surgical and Medical Procedures	**0 [0.00]**	**0.0% (0/497)**	**1 [0.21]**	**0.2% (1/503)**
Cardiac Pacemaker Replacement	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Vascular Disorders	**35 [7.55]**	**5.0% (25/497)**	**20 [4.29]**	**3.6% (18/503)**
Aortic Aneurysm	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Bleeding Varicose Vein	2 [0.43]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Embolism	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Extremity Necrosis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Hematoma	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Hypertension	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Hypertensive Crisis	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
Hypotension	14 [3.02]	2.6% (13/497)	11 [2.36]	2.2% (11/503)
Lymphoedema	2 [0.43]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Orthostatic Hypotension	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
Peripheral Arterial Occlusive Disease	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Peripheral Vascular Disorder	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
Shock	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Thrombosis	5 [1.08]	0.8% (4/497)	3 [0.64]	0.4% (2/503)
Total	**729 [157.3]**	**56.7% (282/497)**	**799 [171.3]**	**53.3% (268/503)**

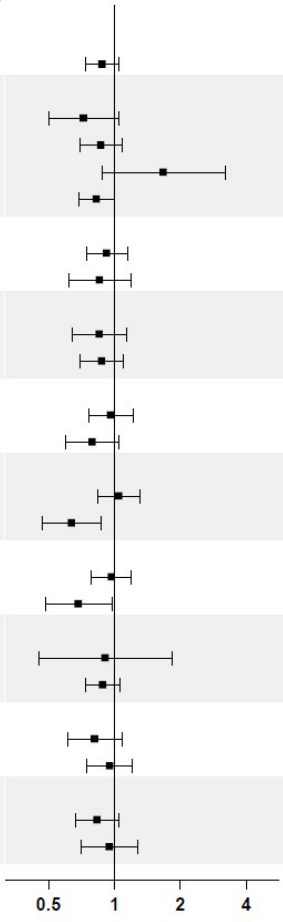
[1]Rate is number of events per 100 subject years.

3. Subgroup Analyses

The primary endpoint was evaluated in subgroups of NYHA Class, qualifying category, ejection fraction, age, sex, race, ethnicity, ischemic cardiomyopathy, and prior cardiac device implant. Figures 9 and 10 show the forest plots for all follow-up and pre-COVID 19, respectively. Women notably derived more benefit than men with 36% reduction in primary endpoint events. African American subjects also gained a larger treatment effect, though minorities (African American and Hispanic subjects) in both the Treatment group and the Control group experienced high rates of primary endpoint events.

Figure 9. Subgroup Analyses – All Follow-up

Subgroup	N	Treatment Events (Rate)	Control Events (Rate)	HR (95% CI)	Subgroup p-value	Interaction p-value
Overall	1000	253 (0.563)	289 (0.640)	0.88 (0.74, 1.05)	0.16	
NYHA Class						
NYHA Class II	296	53 (0.401)	75 (0.554)	0.72 (0.50, 1.05)	0.086	0.095
NYHA Class III*	650	171 (0.589)	198 (0.677)	0.87 (0.70, 1.08)	0.21	
NYHA Class IV	54	29 (1.527)	16 (0.910)	1.68 (0.88, 3.20)	0.12	
NYHA Class II and III	946	224 (0.525)	273 (0.633)	0.83 (0.69, 1.00)	0.050	0.046†
Qualification						
HFH in year prior	557	181 (0.757)	212 (0.820)	0.92 (0.74, 1.14)	0.47	0.71
Elevated BNP/NT pro-BNP only	442	72 (0.350)	77 (0.409)	0.86 (0.62, 1.19)	0.36	
Ejection Fraction						
HFpEF (EF>40%)*	469	90 (0.442)	114 (0.518)	0.85 (0.64, 1.14)	0.28	0.90
HFrEF (EF≤40%)*	531	163 (0.677)	175 (0.773)	0.88 (0.70, 1.10)	0.26	
Age						
Below Median (<71 Years)*	492	156 (0.730)	173 (0.758)	0.96 (0.76, 1.22)	0.75	0.30
Median and Above (≥71 Years)*	508	97 (0.420)	116 (0.529)	0.79 (0.60, 1.05)	0.11	
Sex						
Men*	625	178 (0.656)	171 (0.625)	1.05 (0.84, 1.31)	0.67	0.010
Women*	375	75 (0.434)	118 (0.681)	0.64 (0.47, 0.87)	0.004	
Race						
Caucasian*	807	189 (0.516)	194 (0.531)	0.97 (0.79, 1.20)	0.78	0.095
African American*	179	60 (0.811)	94 (1.184)	0.68 (0.48, 0.97)	0.035	
Ethnicity						
Hispanic*	33	18 (1.257)	21 (1.383)	0.91 (0.45, 1.83)	0.79	0.95
Non-Hispanic*	960	232 (0.544)	264 (0.615)	0.88 (0.73, 1.07)	0.20	
Ischemic Cardiomyopathy						
Ischemic*	397	99 (0.545)	112 (0.670)	0.81 (0.61, 1.08)	0.16	0.40
Non-Ischemic*	560	142 (0.578)	160 (0.607)	0.95 (0.75, 1.21)	0.69	
Device Implant						
With CRT-D/CRT-P/ICD*	562	162 (0.633)	188 (0.759)	0.83 (0.67, 1.04)	0.11	0.48
Without CRT-D/CRT-P/ICD *	438	91 (0.482)	101 (0.508)	0.95 (0.71, 1.28)	0.73	

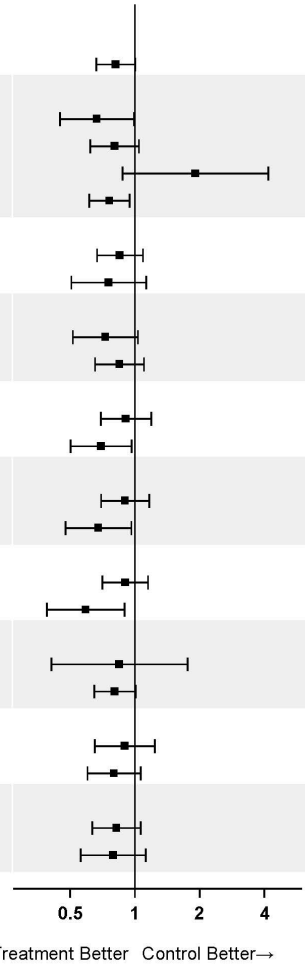


*Pre-specified subgroup

†Interaction p-value testing Randomization Group by NYHA Class II and III vs. Class IV

Figure 10. Subgroup Analyses – Prior to COVID-19

Subgroup	N	Treatment Events (Rate)	Control Events (Rate)	HR (95% CI)	Interaction p-value
Overall	1000	177 (0.595)	224 (0.730)	0.81 (0.66, 1.00)	
NYHA Class					
NYHA Class II	296	43 (0.393)	70 (0.591)	0.67 (0.45, 0.99)	0.074
NYHA Class III	650	114 (0.552)	141 (0.686)	0.80 (0.62, 1.04)	
NYHA Class IV	54	20 (3.123)	13 (1.632)	1.91 (0.88, 4.18)	
NYHA Class II and III	946	157 (0.497)	211 (0.653)	0.76 (0.61, 0.95)	0.035*
Qualification					
HFH in year prior	557	133 (0.771)	166 (0.905)	0.85 (0.67, 1.09)	0.58
Elevated BNP/NT pro-BNP only	442	44 (0.358)	58 (0.474)	0.76 (0.51, 1.13)	
Ejection Fraction					
HFpEF (EF>40%)	469	57 (0.401)	85 (0.551)	0.73 (0.51, 1.03)	0.50
HFrEF (EF≤40%)	531	120 (0.738)	139 (0.870)	0.85 (0.65, 1.10)	
Age					
Below Median (<71 Years)	492	112 (0.746)	130 (0.820)	0.91 (0.69, 1.19)	0.22
Median and Above (≥71 Years)	508	65 (0.442)	94 (0.635)	0.70 (0.50, 0.97)	
Sex					
Men	625	121 (0.687)	139 (0.763)	0.90 (0.70, 1.17)	0.21
Women	375	56 (0.462)	85 (0.683)	0.68 (0.48, 0.96)	
Race					
White	807	135 (0.607)	154 (0.673)	0.90 (0.71, 1.15)	0.091
Black	179	38 (0.721)	70 (1.221)	0.59 (0.39, 0.89)	
Ethnicity					
Hispanic	33	17 (1.575)	19 (1.860)	0.85 (0.41, 1.76)	0.84
Non-Hispanic	960	157 (0.586)	202 (0.726)	0.81 (0.65, 1.01)	
Ischemic Cardiomyopathy					
Ischemic	397	83 (0.682)	87 (0.760)	0.90 (0.65, 1.24)	0.61
Non-Ischemic	560	91 (0.526)	125 (0.658)	0.80 (0.60, 1.06)	
Device Implant					
With CRT-D/CRT-P/ICD	562	117 (0.776)	144 (0.945)	0.82 (0.63, 1.06)	0.92
Without CRT-D/CRT-P/ICD	438	60 (0.424)	80 (0.535)	0.79 (0.56, 1.12)	



*Interaction p-value testing Randomization Group by NYHA Class II and III vs. Class IV

Within the subgroup analyses, an interaction was observed for NYHA class, with the subgroup of NYHA Class IV patients (N = 54) demonstrating a different treatment effect than NYHA Class II and/or III patients. NYHA Class II/III patients overall demonstrated a 24% reduction in primary endpoint events prior to COVID-19 (HR 0.76, 95% CI 0.61-0.95) while NYHA Class IV patients did worse with hemodynamic-guided HF therapy during the same period (HR 1.91, CI 0.88-4.18). The NYHA Class sensitivity analysis demonstrated an interaction p-value of p=0.035, and separate analysis for each NYHA Class is provided below.

NYHA Class II

The baseline demographics and key characteristics for the NYHA Class II patients in the Treatment group and the Control group were balanced and listed in

Table 14 below.

Table 14. Demographics and Baseline Assessments – NYHA Class II Subjects

	Treatment (N=146)	Control (N=150)
Age - yr	69.8 ± 10.9 (146)	69.8 ± 10.5 (150)
Female Sex	33.6% (49/146)	34.0% (51/150)
Race		
White	84.2% (123/146)	82.0% (123/150)
Black	15.1% (22/146)	17.3% (26/150)
Other	0.7% (1/146)	0.7% (1/150)
Ethnicity		
Hispanic	2.7% (4/146)	4.0% (6/150)
Non-Hispanic	95.2% (139/146)	96.0% (144/150)
Unknown	2.1% (3/146)	0.0% (0/150)
Body mass index - kg/m^2	30.7 ± 7.3 (146)	32.5 ± 7.4 (150)
Medical History		
Ischemic etiology	43.2% (63/146)	45.3% (68/150)
Diabetes	49.3% (72/146)	44.7% (67/150)
Atrial flutter or fibrillation	56.8% (83/146)	58.0% (87/150)
Vital Signs and Hemodynamic Analyses		
Left ventricular ejection fraction - %	39.2 ± 17.2 (146)	39.8 ± 16.1 (150)
Left ventricular ejection fraction > 40%	42.5% (62/146)	44.0% (66/150)
Pulmonary capillary wedge pressure - mmHg	16.9 ± 8.2 (145)	17.7 ± 8.4 (150)
Cardiac output - L/min	4.61 ± 1.30 (146)	4.51 ± 1.10 (150)
Cardiac index - L/min/m^2	2.27 ± 0.61 (146)	2.14 ± 0.48 (150)
Laboratory Analyses		
Serum creatinine level - µmol/L	123.1 ± 40.7 (146)	128.3 ± 44.7 (144)
Estimated glomerular filtration rate - ml/min/1.73m^2	56.7 ± 21.5 (146)	54.6 ± 19.2 (143)
B-type natriuretic peptide level - pg/mL	472.8 ± 480.3 (61)	525.4 ± 727.7 (69)
N-terminal pro-B-type natriuretic peptide level - pg/mL	2526 ± 3842 (76)	1537 ± 985 (72)
Treatment History		
Previous cardiac resynchronization therapy	26.7% (39/146)	35.3% (53/150)
Previous implantation of defibrillator	49.3% (72/146)	40.0% (60/150)
Guideline-Directed Medical Therapy		
ACE-Inhibitor or ARB or ARNi	69.2% (101/146)	70.0% (105/150)
ARNi	32.9% (48/146)	30.0% (45/150)
Beta Blocker	89.7% (131/146)	91.3% (137/150)
Mineralocorticoid Receptor Antagonist	43.2% (63/146)	33.3% (50/150)
Diuretic	90.4% (132/146)	93.3% (140/150)
Hydralazine	11.6% (17/146)	20.0% (30/150)
Nitrate	17.8% (26/146)	16.7% (25/150)
SGLT2 Inhibitor	2.2% (1/46)	0.0% (0/41)
Enrollment Type		
Heart failure hospitalization in year prior only	32.2% (47/146)	32.7% (49/150)
Elevated natriuretic peptide level in 30 day prior only	50.7% (74/146)	49.3% (74/150)
Heart failure hospitalization in year prior and elevated natriuretic peptide level in 30 day prior	17.1% (25/146)	18.0% (27/150)

Patient Reported Outcomes		
KCCQ-12 at Baseline - Overall Summary Score	69.7 ± 20.7 (145)	66.4 ± 20.5 (147)
6MHW as Baseline - m	285.5 ± 111.3 (142)	264.8 ± 120.3 (146)

Continuous Variables: Mean ± SD (n); Categorical Variables: Percent (n/N)

The primary endpoint event rates and components for NYHA Class II subjects for the full follow-up and prior to COVID-19 are presented in Table 15 below. Before the pandemic, there were 43 primary endpoint events in the Treatment group compared with 70 events in the Control group, representing a 33% reduction in the 12-month rate of primary endpoint events (0.393 events per patient in the Treatment group vs. 0.591 events per patient in the Control group, HR 0.67).

Table 15. Primary Endpoint and Components – NYHA Class II Subjects

Endpoint[1]	**Treatment (N=146) Events (Rate[2])**	**Control (N=150) Events (Rate[2])**	**Hazard Ratio (95% CI)[3]**
Full Follow-Up			
Heart Failure Hospitalization + ED/OP + Death (Primary Endpoint)	**53 (0.401)**	**75 (0.554)**	**0.72 (0.50, 1.05)**
Heart Failure Hospitalization + ED/OP	42 (0.317)	67 (0.493)	0.64 (0.43, 0.96)
Heart Failure Hospitalization	39 (0.298)	56 (0.417)	0.71 (0.47, 1.09)
HF Emergency Department/Hospital Outpatient Visit (ED/OP)	3 (0.025)	11 (0.089)	0.28 (0.08, 0.99)
Death	11 (0.086)	8 (0.061)	1.39 (0.56, 3.46)
Prior to COVID-19			COVID-19 Interaction p-value[4], p=0.1579
Heart Failure Hospitalization + ED/OP + Death (Primary Endpoint)	**43 (0.393)**	**70 (0.591)**	**0.67 (0.45, 0.99)**
Heart Failure Hospitalization + ED/OP	33 (0.307)	62 (0.531)	0.58 (0.37, 0.89)
Heart Failure Hospitalization	30 (0.276)	51 (0.433)	0.64 (0.40, 1.01)
HF Emergency Department/Hospital Outpatient Visit (ED/OP)	3 (0.038)	11 (0.128)	0.30 (0.08, 1.06)
Death	10 (0.099)	8 (0.074)	1.34 (0.53, 3.39)

[1]Endpoints include CEC adjudicated Heart Failure (HF) Hospitalizations or HF Emergency Department/Hospital Outpatient Visits (ED/OP) with an admission date after the date of implant hospitalization discharge through 395 days after the date of implant. All Cause Deaths are included from implant date to 395 days after implant date.
[2]Event Rate is an annualized rate estimated from the Andersen-Gill model.
[3]Hazard Ratio and 95% Confidence Interval estimated from the Andersen-Gill model with robust sandwich variance estimates. [4]Interaction p-value is a joint test on the interaction term of treatment group by COVID analysis time period.

NYHA Class III

Table 16 presents the baseline demographics and key characteristics for the NYHA Class II patients in the Treatment group and the Control group.

Table 16. Demographics and Baseline Assessments – NYHA Class III Subjects

	Treatment (N=322)	Control (N=328)
Age - yr	68.8 ± 11.3 (322)	69.0 ± 11.2 (328)
Female Sex	39.8% (128/322)	38.7% (127/328)
Race		
White	80.7% (260/322)	79.6% (261/328)
Black	17.7% (57/322)	19.5% (64/328)
Other	1.8% (6/322)	1.2% (4/328)
Ethnicity		
Hispanic	3.7% (12/322)	2.7% (9/328)
Non-Hispanic	96.0% (309/322)	96.6% (317/328)
Unknown	0.3% (1/322)	0.6% (2/328)
Body mass index - kg/m^2	33.9 ± 8.4 (322)	34.2 ± 8.5 (328)
Medical History		
Ischemic etiology	40.7% (131/322)	35.1% (115/328)
Diabetes	48.1% (155/322)	56.1% (184/328)
Atrial flutter or fibrillation	61.8% (199/322)	57.9% (190/328)
Vital Signs and Hemodynamic Analyses		
Left ventricular ejection fraction - %	39.9 ± 17.2 (322)	41.0 ± 17.3 (328)
Left ventricular ejection fraction > 40%	47.2% (152/322)	50.6% (166/328)
Pulmonary capillary wedge pressure - mmHg	17.2 ± 7.9 (321)	17.4 ± 7.6 (328)
Cardiac output - L/min	4.96 ± 3.11 (322)	4.76 ± 1.59 (328)
Cardiac index - L/min/m^2	2.29 ± 1.30 (322)	2.20 ± 0.67 (328)
Laboratory Analyses		
Serum creatinine level - µmol/L	129.1 ± 44.2 (320)	134.5 ± 49.3 (326)
Estimated glomerular filtration rate - ml/min/1.73m^2	53.7 ± 21.0 (320)	52.5 ± 21.6 (326)
B-type natriuretic peptide level - pg/mL	550.8 ± 763.1 (181)	573.9 ± 1054.3 (176)
N-terminal pro-B-type natriuretic peptide level - pg/mL	2258 ± 3316 (133)	2431 ± 3235 (140)
Treatment History		
Previous cardiac resynchronization therapy	28.3% (91/322)	30.5% (100/328)
Previous implantation of defibrillator	40.4% (130/322)	41.5% (136/328)
Guideline-Directed Medical Therapy		
ACE-Inhibitor or ARB or ARNi	62.1% (200/322)	61.9% (203/328)
ARNi	27.3% (88/322)	26.5% (87/328)
Beta Blocker	89.8% (289/322)	87.2% (286/328)
Mineralocorticoid Receptor Antagonist	49.7% (160/322)	46.3% (152/328)
Diuretic	97.2% (313/322)	95.7% (314/328)
Hydralazine	17.4% (56/322)	14.0% (46/328)
Nitrate	20.8% (67/322)	22.6% (74/328)
SGLT2 Inhibitor	1.0% (1/98)	2.2% (2/92)
Enrollment Type		
Heart failure hospitalization in year prior only	35.7% (115/322)	40.1% (131/327)
Elevated natriuretic peptide level in 30 day prior only	44.4% (143/322)	40.4% (132/327)
Heart failure hospitalization in year prior and elevated natriuretic peptide level in 30 day prior	19.9% (64/322)	19.6% (64/327)
Patient Reported Outcomes		
KCCQ-12 at Baseline - Overall Summary Score	49.7 ± 23.1 (320)	50.7 ± 23.3 (325)

6MHW as Baseline - m	218.9 ± 116.1 (306)	218.1 ± 121.4 (312)

Continuous Variables: Mean ± SD (n); Categorical Variables: Percent (n/N)

Table 17 presents the primary endpoint event rates and components for NYHA Class III subjects for the full follow-up and prior to COVID-19. Before the pandemic, there were 114 primary endpoint events in the Treatment group compared with 141 events in the Control group. The difference represents a 20% reduction in the 12-month rate of primary endpoint events (0.552 events per patient in the Treatment group vs. 0.686 events per patient in the Control group, HR 0.80).

Table 17. Primary Endpoint and Components – NYHA Class III Subjects

Endpoint[1]	Treatment (N=322) Events (Rate[2])	Control (N=328) Events (Rate[2])	Hazard Ratio (95% CI)[3]
Full Follow-Up			
Heart Failure Hospitalization + ED/OP + Death (Primary Endpoint)	**171 (0.589)**	**198 (0.677)**	**0.87 (0.70, 1.08)**
Heart Failure Hospitalization + ED/OP	147 (0.502)	171 (0.580)	0.86 (0.69, 1.09)
Heart Failure Hospitalization	127 (0.431)	156 (0.526)	0.82 (0.64, 1.04)
HF Emergency Department/Hospital Outpatient Visit (ED/OP)	20 (0.073)	15 (0.054)	1.34 (0.68, 2.62)
Death	24 (0.089)	27 (0.100)	0.90 (0.52, 1.55)
Prior to COVID-19			COVID-19 Interaction p-value[4], p=0.2840
Heart Failure Hospitalization + ED/OP + Death (Primary Endpoint)	**114 (0.552)**	**141 (0.686)**	**0.80 (0.62, 1.04)**
Heart Failure Hospitalization + ED/OP	96 (0.460)	126 (0.606)	0.76 (0.58, 1.00)
Heart Failure Hospitalization	81 (0.389)	115 (0.555)	0.70 (0.52, 0.94)
HF Emergency Department/Hospital Outpatient Visit (ED/OP)	15 (0.077)	11 (0.057)	1.36 (0.62, 2.97)
Death	18 (0.108)	15 (0.091)	1.19 (0.60, 2.36)

[1]Endpoints include CEC adjudicated Heart Failure (HF) Hospitalizations or HF Emergency Department/Hospital Outpatient Visits (ED/OP) with an admission date after the date of implant hospitalization discharge through 395 days after the date of implant. All Cause Deaths are included from implant date to 395 days after implant date.
[2]Event Rate is an annualized rate estimated from the Andersen-Gill model.
[3]Hazard Ratio and 95% Confidence Interval estimated from the Andersen-Gill model with robust sandwich variance estimates.
[4]Interaction p-value is a joint test on the interaction term of treatment group by COVID analysis time period.

NYHA Class IV

Table 18 presents the baseline demographics and key characteristics for the NYHA Class IV patients (N = 54).

Table 18. Demographics and Baseline Assessments – NYHA Class IV Subjects

	Treatment (N=29)	Control (N=25)
Age - yr	70.3 ± 8.8 (29)	67.3 ± 12.2 (25)
Female Sex	34.5% (10/29)	40.0% (10/25)
Race		
White	69.0% (20/29)	84.0% (21/25)
Black	27.6% (8/29)	12.0% (3/25)
Other	3.4% (1/29)	4.0% (1/25)
Ethnicity		
Hispanic	0.0% (0/29)	8.0% (2/25)
Non-Hispanic	100.0% (29/29)	88.0% (22/25)
Unknown	0.0% (0/29)	4.0% (1/25)
Body mass index - kg/m^2	33.4 ± 10.0 (29)	37.0 ± 11.2 (25)
Medical History		
Ischemic etiology	44.8% (13/29)	28.0% (7/25)
Diabetes	55.2% (16/29)	40.0% (10/25)
Atrial flutter or fibrillation	62.1% (18/29)	56.0% (14/25)
Vital Signs and Hemodynamic Analyses		
Left ventricular ejection fraction - %	34.1 ± 17.8 (29)	42.2 ± 16.7 (25)
Left ventricular ejection fraction > 40%	34.5% (10/29)	52.0% (13/25)
Pulmonary capillary wedge pressure - mmHg	19.6 ± 9.1 (29)	18.5 ± 8.5 (25)
Cardiac output - L/min	4.40 ± 1.16 (29)	4.98 ± 1.61 (25)
Cardiac index - L/min/m^2	2.08 ± 0.53 (29)	2.23 ± 0.74 (25)
Laboratory Analyses		
Serum creatinine level - µmol/L	148.9 ± 58.7 (29)	149.9 ± 56.2 (25)
Estimated glomerular filtration rate - ml/min/1.73m^2	49.3 ± 23.0 (29)	45.3 ± 17.2 (25)
B-type natriuretic peptide level - pg/mL	386.8 ± 482.7 (19)	378.9 ± 329.9 (11)
N-terminal pro-B-type natriuretic peptide level - pg/mL	4653 ± 6525 (10)	3092 ± 3946 (13)
Treatment History		
Previous cardiac resynchronization therapy	41.4% (12/29)	40.0% (10/25)
Previous implantation of defibrillator	37.9% (11/29)	36.0% (9/25)
Guideline-Directed Medical Therapy		
ACE-Inhibitor or ARB or ARNi	62.1% (18/29)	48.0% (12/25)
ARNi	31.0% (9/29)	28.0% (7/25)
Beta Blocker	82.8% (24/29)	76.0% (19/25)
Mineralocorticoid Receptor Antagonist	48.3% (14/29)	56.0% (14/25)
Diuretic	100.0% (29/29)	96.0% (24/25)
Hydralazine	27.6% (8/29)	16.0% (4/25)
Nitrate	20.7% (6/29)	16.0% (4/25)
SGLT2 Inhibitor	0.0% (0/8)	0.0% (0/7)
Enrollment Type		
Heart failure hospitalization in year prior only	27.6% (8/29)	44.0% (11/25)
Elevated natriuretic peptide level in 30 day prior only	44.8% (13/29)	24.0% (6/25)
Heart failure hospitalization in year prior and elevated natriuretic peptide level in 30 day prior	27.6% (8/29)	32.0% (8/25)
Patient Reported Outcomes		
KCCQ-12 at Baseline - Overall Summary Score	39.0 ± 20.2 (29)	40.5 ± 22.5 (25)
6MHW as Baseline - m	153.2 ± 119.3 (26)	164.4 ± 108.2 (24)

Continuous Variables: Mean ± SD (n); Categorical Variables: Percent (n/N)

Table 19 presents the primary endpoint event rates and components for NYHA Class IV subjects for the full follow-up and prior to COVID-19. Before the pandemic, there were 20 primary endpoint events in the Treatment group compared with 13 events in the Control group. The hazard ratio was 1.91 with a wide confidence interval.

Table 19. Primary Endpoint and Components – NYHA Class IV Subjects

Endpoint[1]	Treatment (N=29) Events (Rate[2])	Control (N=25) Events (Rate[2])	Hazard Ratio (95% CI)[3]
Full Follow-Up			
Heart Failure Hospitalization + ED/OP + Death (Primary Endpoint)	**29 (1.527)**	**16 (0.910)**	**1.68 (0.88, 3.20)**
Heart Failure Hospitalization + ED/OP	24 (1.337)	14 (0.840)	1.59 (0.80, 3.18)
Heart Failure Hospitalization	19 (1.130)	13 (0.826)	1.37 (0.66, 2.84)
HF Emergency Department/Hospital Outpatient Visit (ED/OP)	5 (0.535)	1 (0.121)	4.43 (0.52, 38.0)
Death	5 (0.279)	2 (0.123)	2.26 (0.44, 11.6)
Prior to COVID-19			COVID-19 Interaction p-value[4], p=0.9455
Heart Failure Hospitalization + ED/OP + Death (Primary Endpoint)	**20 (3.123)**	**13 (1.632)**	**1.91 (0.88, 4.18)**
Heart Failure Hospitalization + ED/OP	18 (3.110)	11 (1.516)	2.05 (0.88, 4.77)
Heart Failure Hospitalization	13 (2.597)	10 (1.493)	1.74 (0.68, 4.43)
HF Emergency Department/Hospital Outpatient Visit (ED/OP)	5 (0.576)	1 (0.128)	4.51 (0.52, 38.9)
Death	2 (0.268)	2 (0.223)	1.20 (0.18, 8.15)

[1]Endpoints include CEC adjudicated Heart Failure (HF) Hospitalizations or HF Emergency Department/Hospital Outpatient Visits (ED/OP) with an admission date after the date of implant hospitalization discharge through 395 days after the date of implant. All Cause Deaths are included from implant date to 395 days after implant date.
[2]Event Rate is an annualized rate estimated from the Andersen-Gill model.
[3]Hazard Ratio and 95% Confidence Interval estimated from the Andersen-Gill model with robust sandwich variance estimates.
[4]Interaction p-value is a joint test on the interaction term of treatment group by COVID analysis time period.

4. Pediatric Extrapolation
   In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 832 investigators of which none were full-time or part-time employees of the sponsor and 22 had disclosable financial interests/arrangements as

defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 20
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 2

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. In the randomized arm of the GUIDE-HF trial, hemodynamic-guided heart failure management using the CardioMEMS device did not significantly improve heart failure outcomes in patients with New York Heart Association (NYHA) class II-IV heart failure. After one year of follow-up, remote PA pressure monitoring resulted in a 12% reduction in the primary composite endpoint of heart failure hospitalizations, urgent HF visits, and mortality. The observed reduction did not reach statistical significance and was largely driven by a 17% reduction in heart failure hospitalizations. There were no significant differences in all-cause mortality or urgent HF visits between hemodynamic guided heart failure management and usual care.

However, the COVID-19 pandemic occurred while the study was ongoing and likely profoundly impacted the study outcomes. Across North America, hospitals saw notable decrease in heart failure hospital admissions during COVID-19 lockdowns.

The reasons and exact magnitude of the decline in HF admissions are debatable, and data from the GUIIDE-HF trial offer some insights. Using the COVID-19 national emergency declaration date (March 13, 2020) as the cut point, the pre-specified COVID-19 impact analysis confirmed a significant interaction when analyzed based on follow-up completed before vs. after the cutoff date. Adjusting for the pandemic, hemodynamic guided HF management was associated with a 19% reduction in the primary endpoint event rate (HR 0.81, 95% CI: 0.66 – 1.0). The annualized rate of HF hospitalization was 0.43 per patient-year in the Treatment groups vs. 0.59 per patient-year in the Control group, and hemodynamic guided HF management prevented 16 HF events per 100 person-year. The observed treatment effect is clinically meaningful. Additional statistical analyses indicated a high likelihood for trial success with sufficient power if not for the pandemic.

Adjusting for the COVID-19 pandemic in the analysis undoubtedly introduced some uncertainties in the assessment of clinical benefit. Further, the benefit appears to be limited to reduction in HF hospitalization only. Heart failure management with remote hemodynamic monitoring did not improve quality of life or functional status when compared to usual care. These uncertainties will need to be addressed by collecting confirmatory clinical data in a post-approval study. The results of the subgroup analysis further suggest that hemodynamic guided heart failure management may not provide any benefit for patients at late stages of heart failure (i.e., NYHA Class IV). Given that the Guide-HF trial only enrolled a small number of NYHA Class IV subjects, the pivotal data does not provide sufficient evidentiary support for its use in these patients.

Overall, the totality of evidence from the pivotal study supports that HF management guided by remote PA pressure monitoring using the CardioMEMS system is effective for reducing heart failure hospitalizations in NYHA Class II or III patients with either prior heart failure hospitalization or recently elevated natriuretic peptides.

B. Safety Conclusions

The risks of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The CardioMEMS PA pressure sensor has been market approved in the U.S. since 2015, and the safety of the device is well characterized and understood. The frequency and nature of complications observed in the GUIDE-HF Randomized pivotal study are in line with the known safety of the device. In a large sample of 1022 patients with a broad range of heart failure, implant success was high (97.8%) and complications were rare (0.8%). Most complications were due to vascular trauma, and none had resulted in death, chronic disability, or device explant. On long term follow-up, there were no new or unanticipated safety signals associated with the device use. The pivotal data support that the CardioMEMS device and HF management guided by information provided by the

device are safe for the intended use population.

C. Benefit-Risk Determination

This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that the probable benefits outweigh the probable risks for using the CardioMEMS System to provide hemodynamic data for heart failure management with the goal of reducing heart failure hospitalizations in NYHA Class II or III heart failure patients who either have been hospitalized for heart failure in the previous year and/or have elevated natriuretic peptides.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIII. CDRH DECISION

CDRH issued an approval order on [date of approval order]. The final clinical conditions of approval cited in the approval order are described below.

In addition to the Annual Report requirements, the sponsor must provide the following data in post-approval study (PAS) reports for each PAS listed below.

The sponsor must obtain approval of the PAS protocol(s) within 7 months from the date of this order. Within 6 months of the receipt of this letter, the sponsor must submit a PMA supplement that includes a complete protocol of the post-approval study described below. The PMA supplement should be clearly labeled as a "PMA Post-Approval Study Protocol" as noted below and submitted to the address below. Please reference the PMA number above to facilitate processing. If there are multiple protocols being finalized after PMA approval, please submit each protocol as a separate PMA supplement.

1. The PAS is a study to collect additional evidence of continued safety and effectiveness in the NYHA Class II patient population. This data may be collected with real world evidence if it meets the criteria described in the FDA Guidance “Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices” (https://www.fda.gov/media/99447/download). The study requirements for this PAS are outlined below:

- Sufficient NYHA Class II patients including a mortality analysis
- Sufficient women enrolled so that an analysis by sex can be pre-specified
- A prespecified analysis for patients with and without a CRT
- Enrollment strategy to promote a balance in patients across ejection fraction and sex
- Consider modification of the protocol response to pulmonary artery (PA) pressures in HFpEF and HFrEF since now there are at least 2 drugs approved for HFpEF and use of SGLT2i is expected to expand

From the time of study protocol approval, the sponsor must meet the following timelines for the study:

- First subject enrolled within 3 months
- 20% of subjects enrolled within 12 months
- 50% of subjects enrolled within 18 months
- 100% of subjects enrolled within 24 months
- Submission of Final study report: 3 months from study completion (i.e. last subject, last follow-up date)

In addition, the sponsor must submit separate periodic reports on the progress of the study as follows:

- PAS Progress Reports every six (6) months until subject enrollment has been completed, and annually thereafter.
- If any enrollment milestones are not met, the sponsor must begin submitting quarterly enrollment status reports (i.e., every 3 months), in addition to the periodic (6-months) PAS Progress Reports, until FDA notifies the sponsor otherwise.

For all other condition of approval studies, the sponsor must submit separate PAS Progress Reports for each study, every six (6) months for the first two (years) and annually thereafter, unless otherwise specified by FDA.

Each PAS report should be submitted to the address below identified as a "PMA Post-Approval Study Report" in accordance with how the study is identified above and bearing the applicable PMA reference number.

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

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.