SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Heart Failure Monitoring System

Device Trade Name: Cordella Pulmonary Artery Sensor System

Device Procode: MOM

Applicant's Name and Address: Endotronix, Inc.
1415 W. Diehl Road Suite 500W
Naperville, IL 60563

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P230040

Date of FDA Notice of Approval: 6/20/2024

Breakthrough Device: N/A

II. INDICATIONS FOR USE

The Cordella Pulmonary Artery Sensor System is intended to measure, record and transmit pulmonary artery pressure (PAP) data from NYHA Class III heart failure patients who are at home on diuretics and guideline-directed medical therapy (GDMT) as well as have been stable for 30 days on GDMT. The device output is meant to aid clinicians in the assessment and management of heart failure, with the goal of reducing heart failure hospitalizations.

III. CONTRAINDICATIONS

The Cordella Pulmonary Artery Sensor 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 Cordella Pulmonary Artery Sensor System labeling.

V. DEVICE DESCRIPTION

The Cordella PA Sensor System is designed to be used with the Cordella Heart Failure System to better connect healthcare professionals and patients with tools for heart failure management.

The Cordella PA Sensor is an implantable blood pressure monitor that permanently resides in the patient's pulmonary artery. With this Sensor, PA pressure can be wirelessly measured from the patient's home on demand. Active management of a patient using PA pressure data from the Cordella Sensor and vital signs and patient-reported symptoms data from Cordella HF System may improve long-term outcomes in patients with NYHA Class III heart failure.

The Cordella PA Sensor System is comprised of the following subsystems:

- Cordella PA Sensor
- Cordella Delivery System
- myCordella Handheld Patient Reader (including Dock)
- Cordella Calibration Equipment (CalEQ)
- Cordella Data Analysis Platform (CDAP)

The Cordella PA Sensor System, schematized in Figure 1 and described in the paragraphs that follow, interfaces with the commercial Cordella HF System to facilitate PA Pressure (PAP) readings at a patient's home and transmission of the results to a care provider for evaluation. The Cordella HF System is a commercially available convenience kit with Bluetooth connected off-the-shelf peripherals for vital signs monitoring (weight, heart rate, systolic blood pressure, and SpO2), myCordella Tablet (running the myCordella Patient App), and the myCordella Patient Management Portal (PMP), that interfaces with the Cordella PA Sensor System as shown in Figure 1.

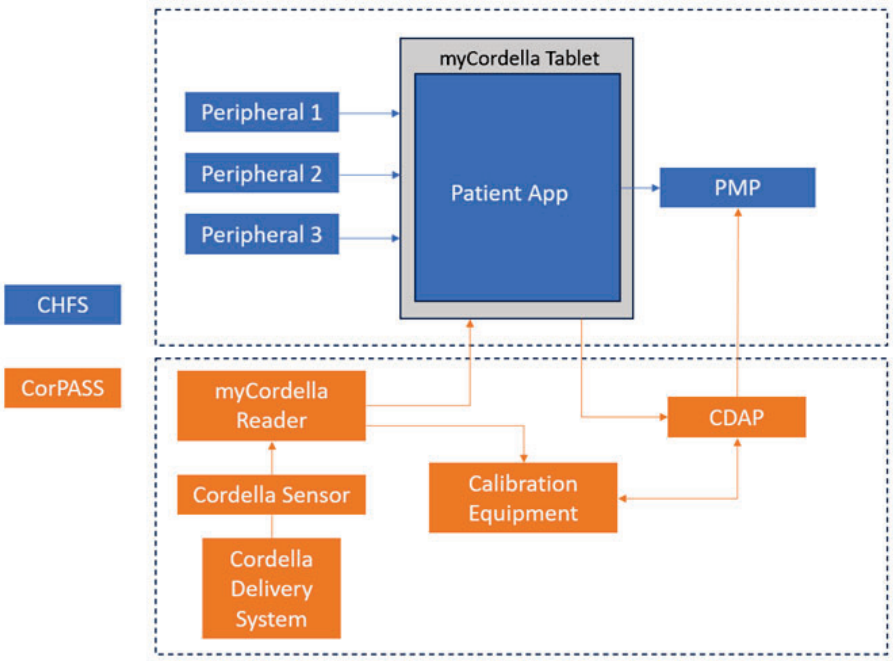


Figure 1: Functional Block Diagram of the Cordella PA Sensor System (CorPASS) and its interface with the Cordella Heart Failure System (CHFS)

The heart of the Cordella PA Sensor System is the **Cordella PA Sensor**, a permanent implant that resides in the patient's interlobar right pulmonary artery, provided that the RPA downturn

diameter is 12-26 mm for secure stabilization of the sensor. The wireless Sensor, illustrated in **Figure 2** and **4**, is a battery-less capacitive pressure sensor packaged in a glass body approximately 20 x 4 x 2 mm in size with a coating of medical grade silicone. Nitinol anchors extend from either end to hold the Sensor body in place against the wall of the pulmonary artery (PA), such that the pressure sensitive surface of the Sensor body faces away from the vessel wall and towards the bloodstream. The Sensor resonates electrically, changing its resonant frequency in proportion to the PAP. The Sensor is shipped sterile to a hospital pre-attached to the distal end of the **Cordella Delivery System**, a custom catheter depicted in **Figure 3**. Attachment wires in the Catheter hold the Sensor's nitinol anchors flat (**Figure 4**) during vascular ingress. A physician uses the Delivery System to place the Sensor via percutaneous venous access in the patient's interlobar right pulmonary artery, provided that the RPA downturn diameter is 12-26 mm for secure stabilization of the sensor. Once placed, the physician uses the Delivery System handle to retract the attachment wires and release the Sensor. At this point, the Sensor's nitinol anchors unfold and hold the device in place for the lifetime of the patient. The Delivery System is removed and discarded following calibration of the Sensor to a fluid-filled reference pressure measurement (described below). The minimally invasive implant procedure is designed to resemble existing Right Heart Catheterization (RHC) procedures, and to be safe..

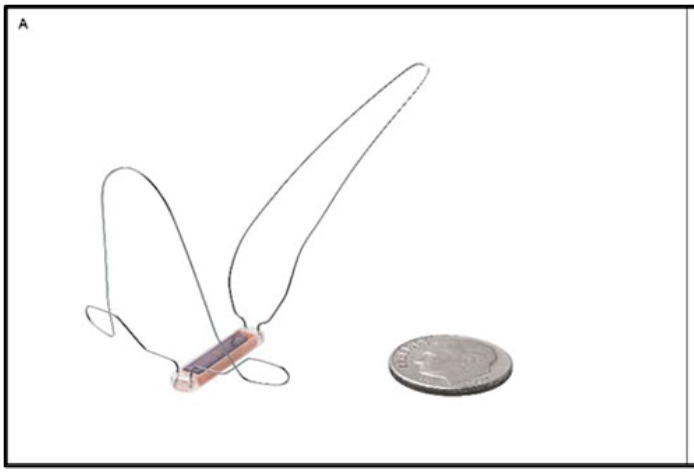


Figure 2: Cordella PA Sensor

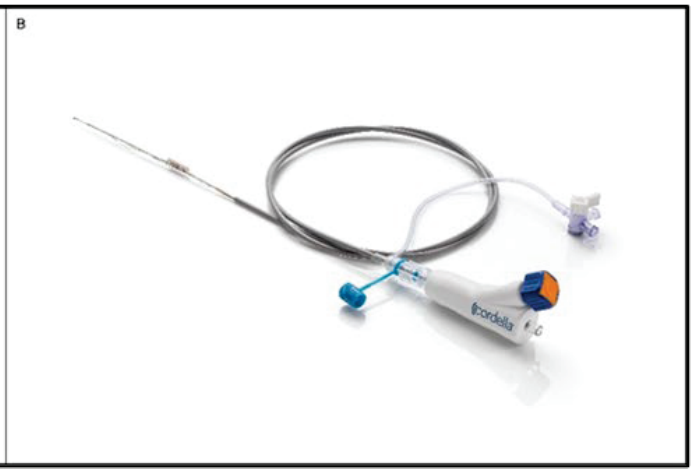


Figure 3: Cordella Delivery System with Sensor

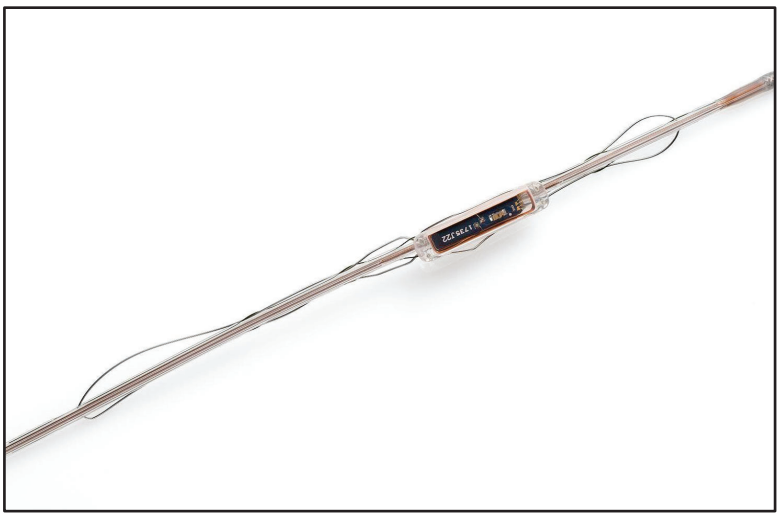


Figure 4: Cordella PA Sensor tied down to Delivery System

The **myCordella Reader (including Dock)** (**Figure 5**) is a handheld wireless device used for obtaining Sensor readings. At home the patient acquires a PAP reading by holding their myCordella Reader against their chest. The Patient App running on an off-the-shelf myCordella Tablet (part of Cordella HF System) provides audio and visual prompts for the patient to guide them through signal acquisition. During the reading, the Reader powers the Sensor wirelessly and obtains the pressure reading by measuring the Sensor frequency that changes in proportion to the pressure on the Sensor. Once the signal is acquired, the patient is notified of the successful reading and the Reader transmits data to the Tablet, where the Patient App connected to the internet using Wi-Fi or cellular transmits the data to the **Cordella Data Analysis Platform (CDAP)**, a web-based application that stores configuration and calibration data, processes raw data from the daily readings, and makes the final PA pressure data (systolic, diastolic, mean pressures and a waveform) available to clinicians through the secure myCordella PMP (also part of Cordella HF System). Changes in PAP can be used in conjunction with vital signs and patient-reported symptoms to guide adjustments to diuretic and other medications. The myCordella Dock connects to a wall plug and recharges the Reader's battery. The entire PA pressure home reading sequence is designed for patient convenience and is generally completed in less than one minute with the entire reading session comprising PA Pressure, vital signs and patient-reported symptoms taking less than 5 minutes. The Reader remains docked at all other times when the patient is not actively taking a reading.

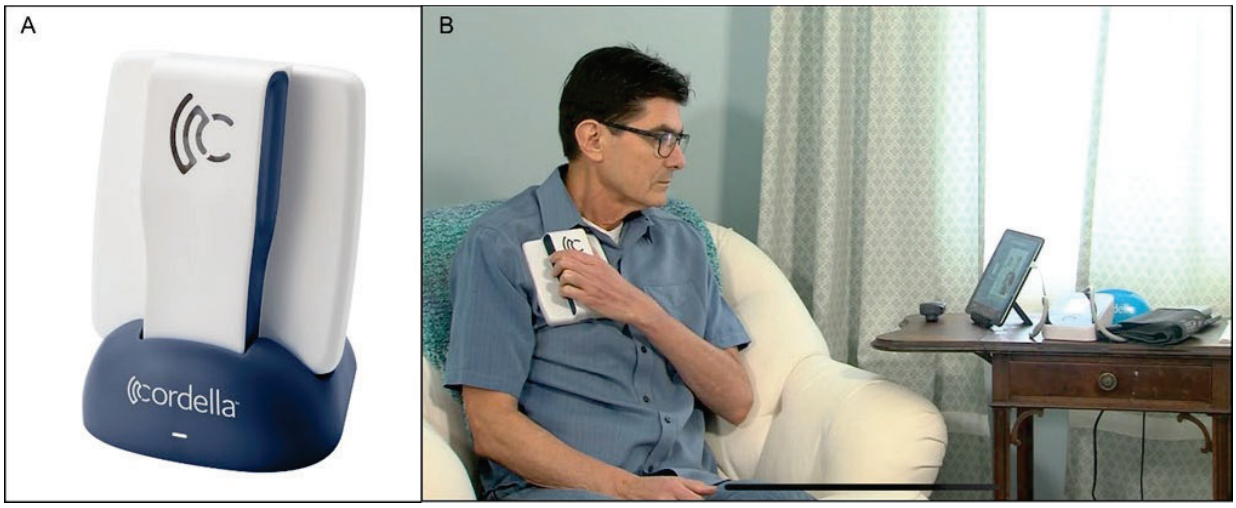


Figure 5A: myCordella Reader and Dock Figure 5B: Depiction of patient taking seated PAP with the myCordella Reader

The ***Calibration Equipment (CalEQ) (Figure 6)*** installed in the cath lab supports the calibration of the Sensor to a reference pressure at the time of implantation.

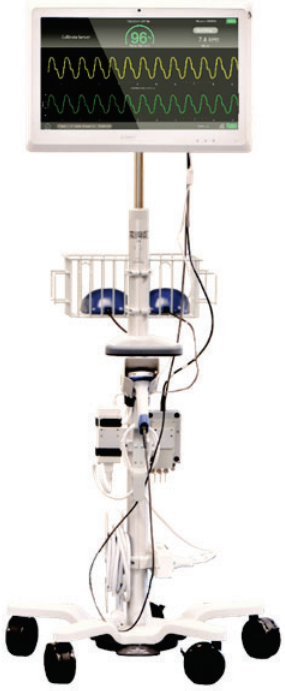


Figure 6: Cordella Calibration Equipment (CalEQ)

Implant Procedure

The Sensor implantation takes place during a minimally invasive RHC that typically takes less than an hour.

Once the target location for the Sensor has been identified in the interlobar right pulmonary artery (provided that the RPA downturn diameter is 12-26 mm for secure stabilization of the sensor), the PA Sensor is deployed. Using the calibration feature in CalEQ, the physician is able to collect simultaneous pressure readings using a reference fluid-filled catheter and the Sensor. The CalEQ software zeroes out any difference in the mean PAP between the reference fluid-filled measurement and the Sensor. **Figure 7** below is a simulated waveform and data presentation available only for the physician during implant.

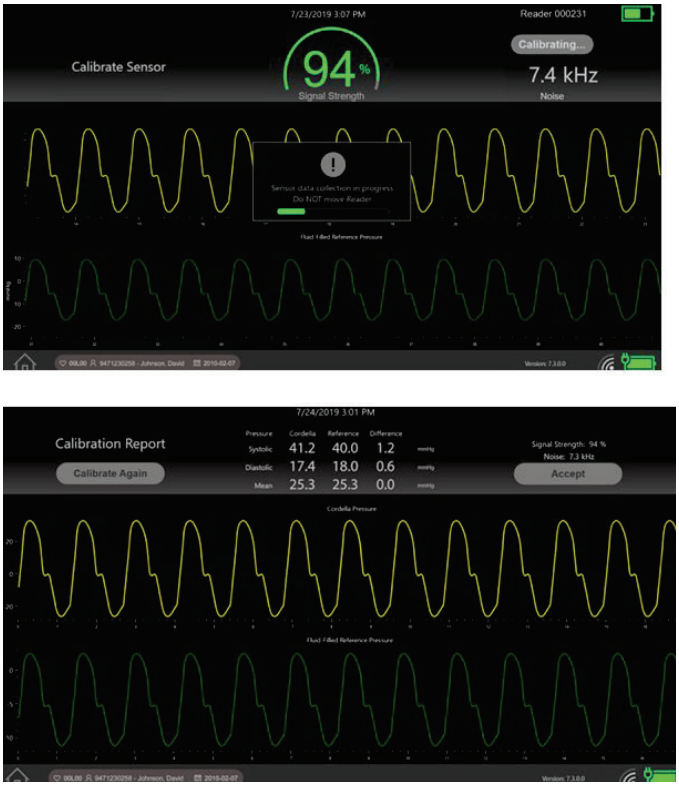


Figure 7: Implanting Physician Interface via the Calibration Equipment

Once the implant procedure is completed, a Reader is given to the patient to take home so that they may begin transmitting pressure readings.

The Cordella PA Sensor System and each of its subsystems only support diagnostic functions. Their purpose is to provide clinicians with accurate PAP data from the patients' home. The system does not recommend therapy or any other clinical action, nor does it draw conclusions from the data.

Notification Algorithm

The CDAP is able to calculate and send to PMP the mean PA pressure (mPAP) trend (7 day average) of a patient and notifications when the patient is outside the target trend range of 5 - 20 mmHg in accordance with the treatment guidelines of the study (Appendix 14.5 in protocol/ CIP Guidelines for managing HF using Pulmonary Artery Pressures). 3 types of notifications are generated consistent with treatment recommendations A, B, and C in the guidelines: "mPAP trend is below target range" when seated mPAP is < 5 mmHg. "mPAP trend is above target range" when seated mPAP is above 20 mmHg, and "mPAP trend is > 10 mmHg above target range" when seated mPAP is over 30 mmHg.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are a couple other alternative methods for obtaining pulmonary artery pressure (PAP) in patients with chronic heart failure.

These methods include a right heart catheterization (RHC) procedure or PAP monitoring with an implantable hemodynamic monitoring system which also gets implanted via a RHC.

A RHC 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. However, use of a RHC procedure to obtain pulmonary artery pressure frequently is impractical and associated with significant risks.

The risks of a RHC either for direct measurements or used for the implantation of a PAP monitoring medical device include entry site complications such as bruising or blood vessel injury, bleeding (during or after the procedure), blood clots and thromboembolisms. Other inherent risks include chest pain or cardiac arrest, induction of cardiac arrhythmias, possible abnormal heart rate (pulse) or heart rhythm, hemoptysis, infection or fever, injury of the valves in the right heart (tricuspid and/or pulmonary), respiratory distress or failure. Of note, this RHC procedure will be performed prior to introduction of the Cordella sensor. However, it will only be done one time.

Of note, insertion of the Cordella PA Sensor is performed via the same RHC procedure described above, as such it exposes the patient to the same peri-procedural risks of a RHC procedure, as described above - albeit for one single procedure, rather than repeated RHC over time.

The primary other implantable pulmonary artery sensor system for the management of heart failure is the CardioMEMS HF System. Each treatment 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 Cordella PA Sensor System has not been marketed in the United States or any foreign country.

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 Cordella Pulmonary Artery Sensor System.

- Allergic reaction
- Arrhythmias
- Bleeding complications (which may require transfusion)
- Cardiac arrest
- Chest pain
- Death
- Device embolization/migration
- Device explant
- Emergent or urgent cardiac, vascular, and/ or other surgery necessitated by the device or implant procedure (e.g., coronary sinus lead revision)
- Endocarditis or device infection
- Entry site complications (e.g., hematoma, dissection)
- Fracture of a component of the device/system that may or may not lead to serious injury or surgical intervention
- Gastrointestinal bleed (secondary to antiplatelet therapy)
- Hemoptysis
- Hypo or hypertension
- Infection or fever
- Lead dislodgement
- Peripheral embolism/thrombus
- Pulmonary embolism/pulmonary occlusion
- Pseudoaneurysm of the vein
- Radiation exposure
- Reaction to contrast media/ medication
- Renal insufficiency or failure
- Respiratory distress or failure (breathing problems)
- Sepsis
- Valvular injury (tricuspid and/or pulmonary)
- Vascular complications (e.g., venous dissection, perforation, rupture, arteriovenous fistula)
- Vessel trauma which may require surgical repair
- Worsening heart failure

For the specific adverse events that occurred in the clinical study, please see Section X

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

Table 1. Summary of Testing – System, Sensor, Delivery System, Reader, and Calibration Equipment

System Functional Testing			
Test	**Acceptance Criteria**	**Results**	**Analysis Type**
System Accuracy (short-term under typical environmental conditions)	System must measure within ± 2 mmHg at baseline (740 mmHg) and ± 3% across the pressure range compared to a reference pressure measurement for a pressure range of 600-860 mmHg (absolute).	PASS	Variable
Worst Case System Error	System Root Sum Square (RSS) error after combining all sources of variation must remain within +/- 7.8 mmHg over 10 years.	PASS	Variable
Sensor Detection Distance	Sensor must be detectable by the Reader up to 16 cm of link distance with ≥ 80% signal strength in air.	PASS	Variable

Sensor Functional Testing			
Test	**Acceptance Criteria**	**Results**	**Analysis Type**
Simulated Use Pressure Cycle Conditions	The Sensor shall meet all safety and functional requirements after 10 years of simulated use (> 400 million cycles).	PASS	Variable for functional requirements Attribute for safety requirements
Temperature Sensitivity	Change in output pressure signal from the Sensor shall be within < -3 mmHg per °C across the range of 36-40°C.	PASS	Variable
Pressure (Over/Under) Exposure	The Sensor shall meet all safety, functional, and accuracy requirements after exposure to high pressure (150 kP/1.5atm) and low pressure (70 kP/0.7 atm) conditions, per ISO 14708-1	PASS	Variable for functional and accuracy requirements Attribute for safety requirements

Mechanical Shock	Sensor must meet safety and functional requirements after vibration, shock, and temperature conditions, per ASTM D4169 and D4332.	PASS	Variable for functional requirements Attribute for safety requirements
Corrosion	The Sensor was tested per ASTM F2129-17b. The metallic components of the Delivery System shall show no signs of corrosion per ISO 10555-1, Clause 4.5.	PASS	Variable for Sensor testing, Attribute for Delivery System testing
Sensor Radiopacity	The Sensor shall be visible under fluoroscopy.	PASS	Attribute

Sensor Compatibility Testing			
Test	**Acceptance Criteria**	**Results**	**Analysis Type**
MRI	Device must meet "MR Conditional" requirements for safe scanning immediately after placement under the following conditions: ● Static magnetic field of 1.5 or 3 Tesla ● Maximum spatial gradient magnetic field of 4000 Gauss/cm (40 T/m) Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2 W/kg for 15 minutes of scanning in the Normal Operating Mode	PASS	Attribute - Third Party Testing and Review
	In non-clinical testing with 1.5 and 3 Tesla systems, device must meet standard requirements for: ● Displacement Force, per ASTM F2052-15 ● RF Heating, per ASTM F2182-11a ● Torque, per ASTM F2213-17 ● Image Artifact, per ASTM F2119-07		
	The Sensor shall meet all safety and functional requirements after exposure to 1.5T and 3T MRI and comply with applicable clauses of ISO/TS 10974.	PASS	Variable for functional requirements

			Attribute for safety requirements
Defibrillation	The Sensor shall meet safety and accuracy requirements after exposure to a defibrillation pulse per ISO 14708-1 part 20.2.	PASS	Attribute
Ultrasound	The Sensor shall meet all safety and functional requirements after exposure to conventional ultrasonic imaging per ISO 14708 section 22.1.	PASS	Attribute
Pacemaker and ICD Compatibility	The Sensor shall meet all safety and accuracy requirements when placed next to commercially available pacemakers, cardiac rhythm management devices, and implantable cardiac defibrillators. The normal operation of the system, pacemakers, and ICD's must not be affected during simultaneous operation for potential modes of use. The in vitro test plan includes: ● Representative relative placement in a human torso anatomical model ● Multiple ICD and pacemaker models ● Variables addressed in the test plan: ○ Number of pacing chambers ○ Potential operating modes ○ Unipolar and bipolar lead configurations ○ Relative orientations between the external system and implanted devices.	PASS	Attribute - Third Party Testing and Review

Delivery System with Sensor			
Test	**Acceptance Criteria**	**Results**	**Analysis Type**
Simulated Implant Procedure Testing	The Cordella PA Pressure Sensor System must meet the following requirements in simulated use testing: 1) The Delivery System shall navigate tortuosity of target vasculature during simulated use. 2) The Delivery System shall be capable of rotating the Sensor at a target location to the desired deployment orientation in a clinically relevant simulated vasculature.	PASS	Attribute

	3) The Delivery System shall be capable of fully deploying the Sensor within +/-1.5 cm and +/- 20° of the target location within a clinically relevant simulated vasculature in the range of vessel diameters and downturn angles. 4) The Sensor shall remain within +/-1.5 cm and +/-20° of the target location after the Delivery System is retracted post Sensor deployment in a clinically relevant simulated vasculature in the range of vessel sizes and downturn angles.		
Catheter Shaft Tensile	Catheter shaft and hub tensile forces must be ≥ 15N. Test performed per ISO 10555-1, Annex B.	PASS	Variable
Catheter Shaft Torsional	When the distal tip of the Delivery System is fixed, the Delivery System shall be able to withstand torsional forces and remain intact during 360 degrees of rotation.	PASS	Attribute
Catheter Shaft Air and Liquid Leakage	Air shall not leak into the hub assembly during aspiration when tested in accordance with ISO 10555-1, Annex D The catheter shall not leak liquid when tested in accordance with ISO 10555-1, Annex C	PASS	Attribute
Catheter Shaft Radiopacity	Parts of the catheter shall be radio-detectable per ISO 10555-1, Clause 4.2.	PASS	Attribute
Pouch Bubble Emission Test	Delivery System pouch shall meet sterile barrier pouch integrity per ISO 11607, testing per ASTM F2096-11.	PASS	Attribute
Pouch Seal Tensile Test	Delivery System pouch seal shall maintain minimum tensile strength per ISO 11607 (≥ 1 lbf), testing per ASTM F88/F88M-15.	PASS	Variable
Delivery System with Sensor			
Test	**Acceptance Criteria**	**Results**	**Analysis Type**
Shipping and Environmental Conditions	The Sensor shall meet all safety and functional requirements after being subjected to simulated transportation and storage conditions per ASTM D4432 and ASTM D4169. The Delivery System shall meet all package integrity, safety and functional requirements after being subjected to simulated transportation and storage conditions per ASTM D4332 and ASTM D4169.	PASS	Variable for Sensor functional requirements Attribute for Sensor safety requirements Variable for pouch seal strength,

			Attribute for bubble emission, safety and functional Delivery System requirements
Shelf-Life	The Sensor should meet all safety and functional requirements after real-time aging of 2 years. The Delivery System should meet package integrity, safety, and functional requirements after real-time aging of 2 years.	PASS	Variable for Sensor functional requirements Attribute for Sensor safety requirements Variable for pouch seal strength, Attribute for bubble emission, safety and functional Delivery System requirements

Sterilization			
Test	**Acceptance Criteria**	**Results**	**Analysis Type**
Sterilization	The Delivery System with attached Sensor shall be EO sterilized and achieve a sterility assurance level (SAL) of 10^{-6} in a sterilization process validation performed per ISO 11135. The hardest-to-sterilize location in the Delivery System does not create a more difficult-to-sterilize area than the non-product EPCDs or IPCDs, which are used as the biological challenge device. A validated EtO sterilization process is used. It is considered an overkill sterilization cycle.	PASS	Attribute - Third Party Testing and Review

Sterilization			
Test	**Acceptance Criteria**	**Results**	**Analysis Type**
	The sterilization process must demonstrate a sterility assurance level of $< 10^{-6}$ using a "worst-case" challenge configuration of the product in a sterilization process validation performed per ISO-11135 requirements		
Sterilization Byproducts	EO residuals must be within acceptable limits per ISO 10993-7.	PASS	Attribute - Third Party Testing and Review

Handheld Reader			
Test	**Acceptance Criteria**	**Results**	**Analysis Type**
Electrical Safety Testing	The system shall be compliant with safety requirements of medical electronics per IEC 60601-1.	PASS	Attribute - Third Party Testing and Review
Emissions Testing (FCC and International)	The Reader shall comply with emissions requirements of FCC Part 15.209.	PASS	Attribute - Third Party Testing and Review
Electromagnetic Compatibility Testing	The Reader shall meet electromagnetic compatibility requirements of AIM RFID Reader Immunity, RED 2014/53/EU, and EMC 2014/30/EU.	PASS	Attribute - Third Party Testing and Review
Design Testing	Reader predicted frequency output should not vary greater than +/- 1.0kHz due to axial rotation of the Reader relative to the Sensor.	PASS	Variable
	Reader predicted frequency output should not vary greater than +/-3.0kHz when Sensor or simulated Sensor position translates up to +/- 2 cm in X and/or Y planes	PASS	Variable
	Reader predicted frequency output should not vary greater than +/- 11.6kHz when subjected to environmental temperatures of +5°C to 40°C AND rH of 15% to 90%, non condensing	PASS	Variable

Handheld Reader			
Test	**Acceptance Criteria**	**Results**	**Analysis Type**
	Reader predicted frequency output should not vary greater than +/- 13.4kHz when the distance between the Sensor and Reader is within the reading window.	PASS	Variable
	Reader predicted frequency output should not vary greater than +/- 11.0kHz across the operating frequency bandwidth of 12.880MHz to 14.120MHz.	PASS	Variable
	Reader predicted frequency output should not vary greater than 0.6kHz throughout the battery operating voltage range.	PASS	Variable
Thermal Assessment Test	The Reader and Dock shall comply with IEC 60601-1 Clause II Protection against excessive temperatures. Reader and Dock must function accurately (within +/- 11.6 kHz of a reference standard) over the range of normal operating temperatures (5ºC to 35ºC) as defined in IEC 60601-1-11 and not exceed surface and internal temperatures as defined by IEC 60601-1.	PASS	Attribute - Third Party Testing and Review
Reader and Dock Functional Lifetime Testing	The Reader and Dock shall continue to meet functional and accuracy requirements through 4 years of simulated use.	PASS	Variable for accuracy requirements, Attribute for functional requirements
Mechanical Testing	The Reader and Dock shall function after rough handling, shock, and vibration for handheld devices as required per IEC 60601-1 and 60601-1-11.	PASS	Attribute - Third Party Testing and Review
Label Durability Testing	The labeling on the Reader shall meet label legibility and durability requirements per IEC 60601-1 Clause 7.1.2 and Clause 7.1.3.	PASS	Attribute - Third Party Testing and Review
Shipping and Environmental Conditions	The Reader and Dock shall meet transport and storage conditions defined by IEC 60601-1-11. Reader shall meet all accuracy and functional requirements after simulated transportation	PASS	Variable for accuracy requirements, Attribute for

Handheld Reader			
Test	**Acceptance Criteria**	**Results**	**Analysis Type**
	conditions within packaging per guidance of ISTA-2A or ASTM D4332 and ASTM D4169. The Dock shall charge the Reader and display charging status after simulated transportation conditions within packaging per guidance of ISTA-2A or ASTM D4332 and ASTM D4169.		functional requirements

Calibration Equipment			
Test	**Acceptance Criteria**	**Results**	**Analysis Type**
Electrical Safety Testing	Calibration Equipment shall meet safety requirements for medical electronic equipment defined by IEC 60601-1.	PASS	Attribute - Third Party Testing and Review
Emissions Testing (FCC and International)	Calibration Equipment shall meet emissions requirements as defined by IEC 60601-1-2 and FCC Part 15.	PASS	Attribute - Third Party Testing and Review
Electromagnetic Compatibility Testing	Calibration Equipment shall meet requirements for electromagnetic compatibility as defined by IEC 60601-1-2.	PASS	Attribute - Third Party Testing and Review
Design Testing	Calibration Equipment should operate on battery power for at least 2 hours.	PASS	Attribute
	Calibration Equipment shall make calibration reading data available within 10 seconds of the completed reading	PASS	Attribute
Calibration Equipment Functional Lifetime Testing	Calibration Equipment shall have a functional lifetime of 5 years.	PASS	Attribute
Mechanical Testing	Calibration Equipment shall maintain basic safety after rough handling and meet stability and transportability requirements per IEC 60601-1.	PASS	Attribute - Third Party Testing and Review

Calibration Equipment			
Test	**Acceptance Criteria**	**Results**	**Analysis Type**
Label Durability Testing	The labeling on the Calibration Equipment shall meet label legibility and durability requirements per IEC 60601-1 Clause 7.1.2 and Clause 7.1.3.	PASS	Attribute - Third Party Testing and Review
Shipping and Environmental Conditioning	N/A - not performed since Calibration Equipment is assembled by Endotronix personnel and 100% inspected upon delivery.	N/A	N/A

The engineering study results for the implantable Sensor demonstrated the following conclusions:

- Remains functional, hermetic and accurate after 10 years of simulated use;
- Temperature, over-pressurization and mechanical shock have a negligible effect on Sensor function;
- Meets its specifications for accuracy during the hermeticity and calibration testing;
- Meets RF signal detection requirements for distance between the Reader and the implanted sensor in a simulation;
- Remains securely attached to the Delivery System during delivery and rotation until release;
- Is resistant to corrosion; and
- Is compatible with MRI, defibrillators, ultrasound, pacemakers, ICDs, and glucose monitors.

The engineering study results for the Delivery System demonstrated the following conclusions:

- May be removed from the packaging, flushed with saline, advanced over an 0.018" or 0.025” guidewire and loaded into a venous sheath;
- Positions the Sensor in the target vessel via femoral or jugular access, rotates and retracts the Sensor as needed before deployment, facilitates reference pressure measurements and releases the Sensor at the appropriate location in the downturn of the pulmonary artery;
- Does not damage the catheter or Sensor during delivery and has sufficient tensile strength to maintain its integrity during use;
- Is corrosion resistant and is sufficiently radiopaque.

Table 2. Biocompatibility

Biocompatibility				
Test		**Acceptance Criteria**	**Results**	**Analysis Type**
Cytotoxicity	Sensor	Meet requirements in an ISO Elution Method study (1xMEM Extract), per ISO 10993-5.	PASS (non-cytotoxic)	Attribute -- Third Party Testing
	Delivery System	Meet requirements in an ISO Elution Method study (1xMEM Extract), per ISO 10993-5.	PASS (non-cytotoxic)	
Sensitization	Sensor	Meet requirements in an ISO Maximization Sensitization Study (Extract), per ISO 10993-10.	PASS (Non-sensitizer)	Attribute -- Third Party Testing
	Delivery System	Meet requirements in an ISO Maximization Sensitization Study (Extract), per ISO 10993-10.	PASS (Non-sensitizer)	
Intracutaneous Reactivity (Irritation)	Sensor	Meet requirements in an ISO Intracutaneous Study (Extract), per ISO 10993-10.	PASS (Non-irritant)	Attribute -- Third Party Testing
	Delivery System	Meet requirements in an ISO Intracutaneous Study (Extract), per ISO 10993-10.	PASS (Non-irritant)	
Acute Systemic Toxicity	Sensor	Meet requirements in an ISO Acute Systemic Toxicity Study (Extract), per ISO 10993-11.	PASS (Non-toxic)	Attribute -- Third Party Testing
	Delivery System	Meet requirements in an ISO Acute Systemic Toxicity Study (Extract), per ISO 10993-11.	PASS (Non-toxic)	
Hemolysis	Sensor	Meet requirements in an In Vitro Hemolysis Study (ASTM-Extraction Method), per ISO 10993-4.	PASS (Non-hemolytic)	Attribute -- Third Party Testing
	Delivery System	Meet requirements in an In Vitro Hemolysis Study (ASTM-Extraction Method), per ISO 10993-4.	PASS (Non-hemolytic)	
SC5b-9 Complement Activation	Sensor	Meet requirements in a complement activation study (SC5b-9), per ISO 10993-4.	PASS (Non-activator)	Attribute -- Third Party Testing
	Delivery System	Meet requirements in a complement activation study (SC5b-9), per ISO 10993-4.	PASS (Non-activator)	
USP Pyrogen Study	Sensor	Meet requirements in a USP Pyrogen Study (Material Mediated), per ISO 10993-11.	PASS (Non-pyrogenic)	Attribute -- Third Party Testing
	Delivery System	Meet requirements in a USP Pyrogen Study (Material Mediated), per ISO 10993-11.	PASS (Non-pyrogenic)	
ASTM Partial Thromboplastin Time (PTT)	Sensor	Meet requirements in a Partial Thromboplastin Time Study (ASTM-Extraction Method), per ISO 10993-4.	PASS (non-activator)	Attribute -- Third Party Testing
	Delivery System	Meet requirements in a Partial Thromboplastin Time Study (ASTM-Extraction Method), per ISO 10993-4.	PASS (non-activator)	

Biocompatibility				
Test		**Acceptance Criteria**	**Results**	**Analysis Type**
Genotoxicity (Bacterial Reverse Mutation)	Sensor	Meet requirements in a bacterial reverse mutation study per ISO 10993-3.	PASS (Non-mutagenic)	Attribute -- Third Party Testing
Genotoxicity (Mouse Lymphoma)	Sensor	Meet requirements in a Mouse Lymphoma Assay study per ISO 10993-3.	PASS (Non-mutagenic)	Attribute -- Third Party Testing
Carcinogenicity	Sensor	Scientific rationale provided for no risk of carcinogenesis associated with clinical use.	PASS	Third Party Review
Subacute/ Subchronic and Chronic Toxicity	Sensor	Scientific rationale provided for waiving subacute, subchronic, and chronic toxicity testing of the Sensor for the following reasons: • Materials are known materials with an established history of biocompatibility in devices with similar applications. The materials are not known to cause systemic toxicity. • No acute systemic toxicity was observed during the acute systemic toxicity study in mice. Additionally, no evidence of systemic toxicity was observed in the clinically relevant (ovine) implantation study at any of the following timepoints: 30, 90, 180, and 365-days. • Chemical characterization and associated toxicological evaluation demonstrated no potential for significant patient exposure to the specific compounds that could pose a potential risk of systemic toxicity. • The results of the cytotoxicity assay indicated that the amounts and types of leachable chemicals from the Sensor are not likely to result in adverse biological effects in *in vivo* long term systemic toxicity studies or clinical use of the device.	PASS	Third Party Review
Thromboresistance, and Histopathology	Sensor	Must demonstrate acceptable long term tissue response and thromboresistance after 12-months implantation in an ovine animal model.	PASS	Attribute -- Third Party Testing

Biocompatibility				
Test		**Acceptance Criteria**	**Results**	**Analysis Type**
				and Review
	Delivery System	*In Vivo* Thromboresistance Study in Sheep Jugular Vein 4 Hours	PASS (thrombo-resistant)	Attribute -- Third Party Testing
Particulate Testing	Sensor	The Sensor and Delivery System shall be compliant with ISO 14708 section 14 for particulates during intended use.	PASS	Variable -- Third Party Testing
	Delivery System	The Sensor and Delivery System shall be compliant with ISO 14708 section 14 for particulates during intended use.	PASS	

Table 3. US and International Standards

Standard Number	**Description**
ISO 11607-1	Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems and packaging systems
ISO 10993	Biological Evaluation of Medical Devices
ASTM F1980-21	Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices
ASTM D4332-14	Standard Practice for Conditioning Containers, Packages, or Packaging Components for Testing
ASTM D4169-22	Standard Practice for Performance Testing of Shipping Containers and Systems
ISO 11135	Sterilization of health-care products - Ethylene oxide - Requirements for the development, validation and routine control of a sterilization process for medical device

Standard Number	Description
ISO 11737-1	Sterilization of health care products — Microbiological methods — Part 1: Determination of a population of microorganisms on products- Amendment 1
ISO 14708-1	Implants for surgery – Active implantable medical devices, Part 1: General requirements for safety, marking and for information to be provided by the manufacturer
IEC 60601-1	Medical electrical equipment - Part 1: General requirements for basic safety and essential performance.
IEC 60601-1-6	Medical electrical equipment - Part 1-6: General requirements for basic safety and essential performance - Collateral standard: Usability
IEC 60601-1-2	Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral standard: Electromagnetic disturbances – Requirements and tests.
IEC 60601-1-11	Medical electrical equipment - Part 1-11: General requirements for basic safety and essential performance - Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment.
IEC 60601-2-34	Medical electrical equipment – Part 2-34: Particular requirements for the basic safety and essential performance of invasive blood pressure monitoring equipment
ISO 14117	Active implantable medical devices -- Electromagnetic compatibility -- EMC test protocols for implantable cardiac pacemakers, implantable cardioverter defibrillators and cardiac resynchronization devices
AIM 7351731	Medical Electrical Equipment & System Electromagnetic Immunity Test for RFID readers.

Standard Number	Description
IEC 61000-4-2	Testing and measurement techniques – Electrostatic discharge immunity test
AAMI TIR69	Technical Information Report Risk Management of Radio-Frequency Wireless Co-existence for Medical Devices and Systems
ISO 10555-1	Intravascular catheters – Sterile and single-use catheters – Part 1: General requirements
ISO 80369-7	Small-bore connectors for liquids and gases in healthcare applications -- Part 7: Connectors for intravascular or hypodermic applications
ASTM F2477-07	Standard Test Methods for in vitro Pulsatile Durability Testing of Vascular Stents
ASTM F2129-17b	Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices
ASTM D1002	Apparent Shear Strength of Single-Lap-Joint Adhesively Bonded Metal Specimens by Tension Loading
ASTM D4896-01	Standard Guide for Use of Adhesive-Bonded Single-Lap-Joint Specimen Test Results
IEC 62304	Medical device software - Software life cycle processes
TIR57	Principles for medical device security – Risk Management
ISO 13485	Medical devices - Quality management systems - Requirements for regulatory purposes
ISO 14644-1	Cleanrooms and associated controlled environments, Part 1: Classification of air cleanliness by particle concentration
ISO 14644-2	Cleanrooms and associated controlled environments, Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration.

Standard Number	Description
ISO 14644-3	Cleanrooms and associated controlled environments - Part 3: Test methods
IEC 62366-1	Medical devices - Part 1: Application of usability engineering to medical devices
ISO/IEC 15459-4	Information technology — Automatic identification and data capture techniques — Unique identification — Part 4: Individual products and product packages

B. Animal Studies

A chronic, GLP animal study was performed in twenty-eight (28) sheep with follow-up periods of 30 days, 90 days, 180 days and 365 days. The results of the animal study indicated that:

- No device related adverse safety outcomes occurred during the survival period and clinical pathology findings were acceptable.
- There were no Sensor displacements or Sensor migrations during the study period (this was confirmed via imaging at every follow up time point).
- Pulmonary artery pressure comparisons between Swan Ganz and the Sensor readings demonstrated Cordella PA Sensor System accuracy at 30 days, 90 days, 180 days and 365 days.
- There was no device related injury along the Delivery System pathway.
- Subchronic systemic toxicity assessment did not show device related changes.
- Implant site histopathology assessment showed low to no inflammation, variable neointimal coverage as expected in a sheep model, and overall acceptable biocompatibility of the Sensor body and anchors.
- Readings were obtained from all Sensors throughout the study.

C. Additional Studies

N/A

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the Cordella Pulmonary Artery Sensor System to guide the treatment of patients with New York Heart Association (NYHA) Class III heart failure in the US under IDE #G190020. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

Feasibility Studies

A. Study Design

SIRONA (ETX-HFS-PA-01; clinicaltrial.gov identifier: NCT03375710) was a multi-center, open-label, first-in-human, feasibility study to evaluate the Cordella HF System and the safety and accuracy of the Cordella PA Sensor System in 15 NYHA Class III patients in Europe. The study met its primary endpoints of safety and accuracy and supported a larger prospective trial powered to test the primary accuracy endpoint at 90 days.[1]

SIRONA 2 (ETX-HFS-PA-02: clinicaltrial.gov identifier: NCT04012944) was a prospective, multi-center, open-label, single-arm trial evaluating the safety and efficacy of the Cordella PA

Sensor System and Cordella HF System in NYHA Class III HF patients in Europe with either HF hospitalization (HFH) and/or an increase in natriuretic peptides in the previous 12 months.[2] The PA sensor was successfully implanted in 70 patients. The primary safety endpoint was freedom from adverse events associated with use of the Cordella PA Sensor System through 30 days post-implant in the intent-to-treat population (N=75). There was a total of 6 (8.0%) adverse events. There were 2 (2.7%) serious adverse events related to the implant procedure with one being classified as device/system-related complication (LV Lead dislodgement), both occurred in the same patient. There were no pressure sensor failures. By 12 months post-implant, there were 10 predefined adverse events in 9 (12.0%) subjects as adjudicated by the clinical events committee and there were no further device/system-related complications nor pressure sensor failures. The primary efficacy endpoint was the accuracy of the PA sensor mPAP measurement compared to fluid-filled catheter (RHC) at 90 days. Equivalence between the PA sensor and RHC for mPAP was excellent with mean difference between the measurements confined within the equivalence bounds of -4.0 to 4.0 mmHg (mPAP: avg diff = 1.4, 90% CI 0.0 to 2.9 mmHg, P = 0.003) (**Figure 8**). Differences between Cordella PA sensor and RHC readings were statistically identical at 90-day and 12-month measurements for supine mPAP (1.4 ± 6.7 vs. 3.0 ± 6.8 mmHg, p = 0.12). Levene's test for equality of variance showed that the variance in measurement accuracy (i.e., measurement error) of the Cordella PA Sensor mPAP, compared to RHC mPAP, did not change from 90-days to 12-months (all p-values > 0.05). **Table 4**.

Figure 8: Two one-sided t-tests (TOST) Plot for Mean Pulmonary Artery Pressure (SIRONA 2)

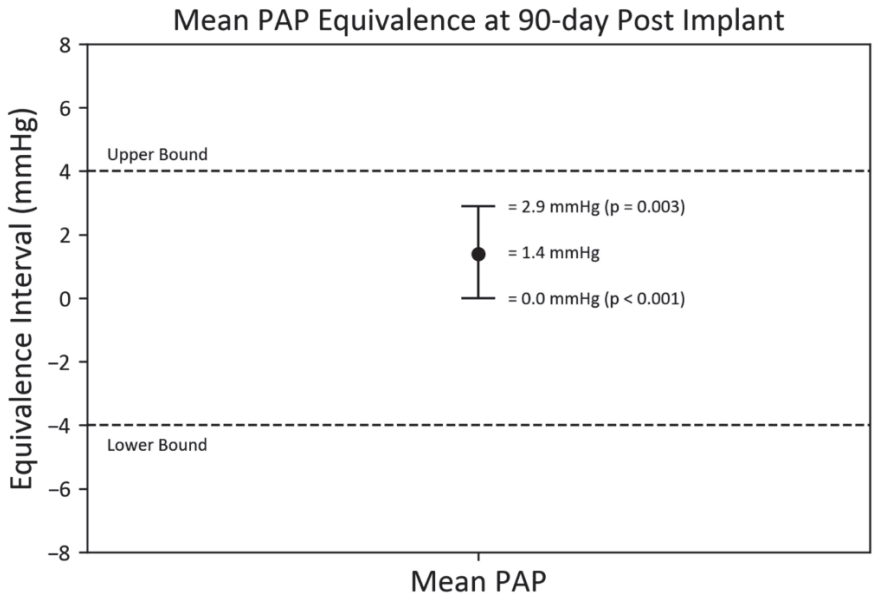


Table 4: Comparison of 90-day and 12-month Supine PAP measures by both PA sensor and RHC

Timepoint	PAP Parameter (mmHg)	PAP Measurement Method	Average ± SD (mmHg)	Levene's Test p-value	Δ (RHC-PA Sensor)	Δ p-value
90-day	Supine Mean PAP	RHC	26.1 ± 10.4	0.13	1.4 ± 6.7	0.12
		Cordella	27.6 ± 12.1			
12-month	Supine Mean PAP	RHC	25.6 ± 10.0	0.77	3.0 ± 6.8	
		Cordella	28.5 ± 10.0			

The results observed during these feasibility studies provided a basis for prospective evaluation of safety and clinical efficacy in larger cohort studies.

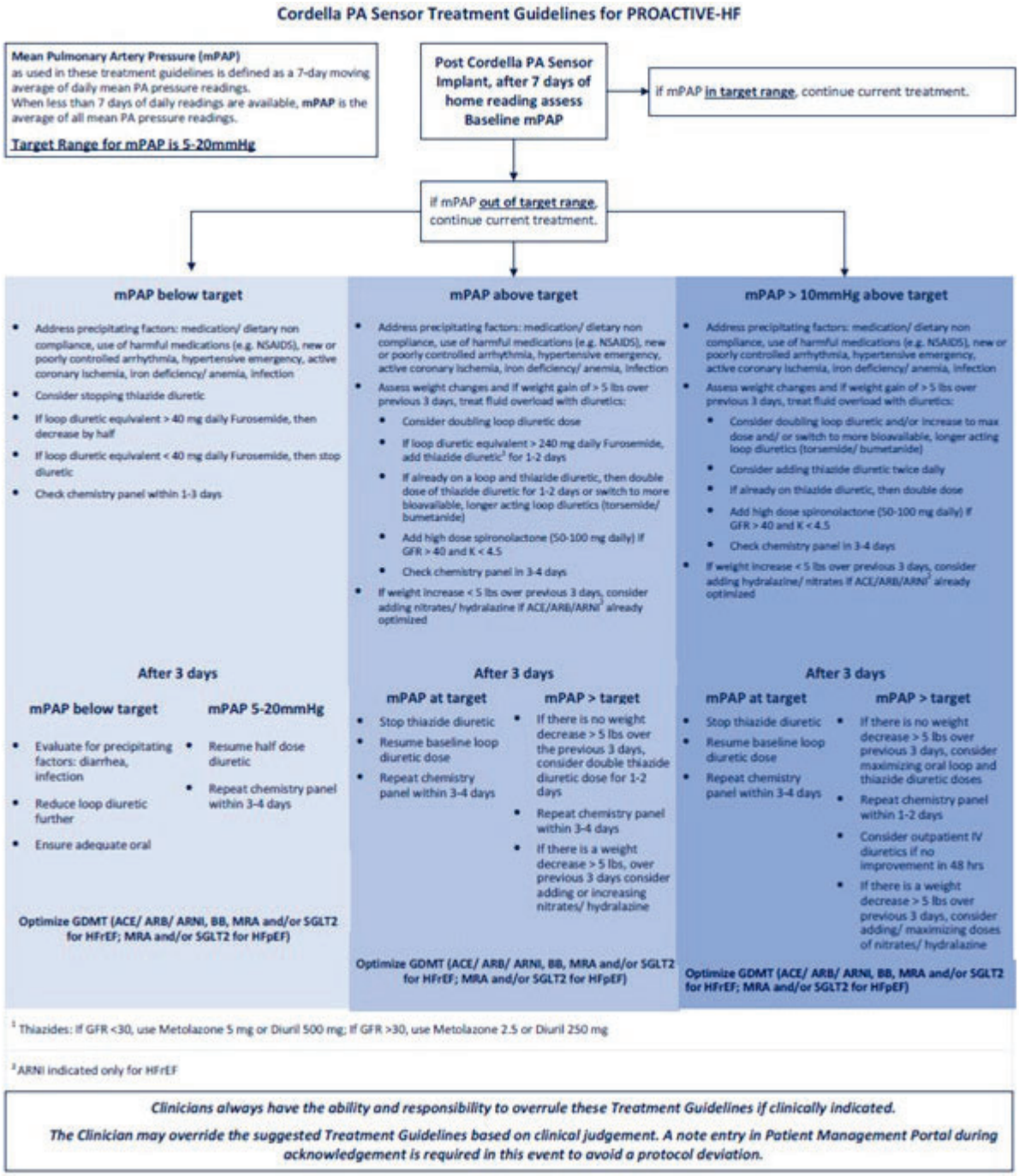
Pivotal Study/ ETX-HFS-PA-03 (PROACTIVE -HF)

Summary / Background

In its final design, the PROACTIVE-HF study was a prospective, single-arm, open-label, multi-center clinical trial to evaluate the safety and effectiveness of the Cordella PA Sensor System in NYHA functional class III HF patients. Adults with a diagnosis of HFrEF or HFpEF and NYHA functional class III symptoms were eligible for enrollment if they were treated with GDMT for a minimum of 3 months (stable doses at least 30 days prior to enrollment) and, within the past year, the patient had either 1) one HF hospitalization, or 2) HF treatment in a hospital day care setting, or 3) urgent outpatient clinic HF visit for IV diuretics, or 4) a persistently elevated NT-proBNP level at the time of screening. The Institutional Review Board of each participating center approved the study protocol, each patient provided written informed consent, and events were adjudicated by a Clinical Events Committee.

All patients enrolled into PROACTIVE-HF received the Cordella HF System (recording weight, BP, HR, and SpO_2). After demonstrating compliance with utilization, all patients underwent right heart catheterization and deployment of the Cordella PA pressure sensor into the interlobar right pulmonary artery, provided that the RPA downturn diameter is 12-26 mm for secure stabilization of the sensor. Patients were instructed to take their daily PAP measurements along with their weight, BP, HR, SpO_2, and HF symptoms by using Bluetooth-connected peripherals. Vital signs were visible to both clinicians and patients, while pulmonary artery pressures were visible to the clinicians only. All patients were then managed according to the trial specific seated mPAP treatment guidelines, with a target seated mean pulmonary artery pressure goal of 5-20 mmHg, achieved through titration of diuretics and GDMT via a trial specific treatment guideline as shown in Figure 9.

Figure 9: PROACTIVE-HF Treatment Guidelines for Seated Mean Pulmonary Artery Pressure



Of note, the aforementioned final study design resulted from a deviation of the original study design for the PROACTIVE-HF, which was initially designed by the manufacturer of this device to be a prospective, randomized, controlled, multi-center clinical trial. In the initial phases of this trial, patients were initially randomized 1:1 to either Control or Treatment groups. All readings

(pulmonary artery pressure and vital signs) were visible to clinicians of patients within the treatment arm, while only the vital signs were visible to treatment arm patients themselves. However, once PROACTIVE-HF began enrolling subjects, prospective clinical evidence from CardioMEMS was published in 2019-2021, including the GUIDE-HF Trial in 2021. The GUIDE-HF Trial was a prospective, randomized, controlled, single-blind, multicenter, pivotal clinical trial whose purpose was 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. The GUIDE-HF Trial demonstrated a positive clinical benefit of PAP-guided heart failure management in NYHA functional class III patients using the CardioMEMS device.[3] With this new evidence, in December 2021 the manufacturer of this device petitioned to the Food and Drug Administration (FDA), to change the study design from a randomized controlled clinical trial to a single-arm trial (described above), with pre-specified safety and efficacy endpoints to provide objective evidence of a similar risk-benefit profile to the CardioMEMS HF System in NYHA functional class III subjects.[6] At the time of crossover to a single-arm, patients in the randomized Control arm (Cohort #1) were unblinded and both clinicians and patients, who opted, in received immediate access to mPAP data and all patients were then managed according to the trial specific seated mPAP treatment guidelines. Cohort #1 subjects did not contribute to the primary safety and efficacy endpoints of PROACTIVE-HF but contributed to a patient engagement substudy. Patients in the randomized Treatment arm (Cohort #2) continued follow-up per protocol and, along with the newly enrolled single arm Treatment group (Cohort #3), contributed to the primary safety and efficacy endpoints of PROACTIVE-HF.

Study Objectives

The objectives of this study are to demonstrate the safety and efficacy of the Cordella PA Sensor System

A. Study Design

Patients were treated between January 10, 2020 and September 30, 2023. The database for this PMA reflected data collected through September 30, 2023 and included 456 patients. There were 77 investigational sites.

This study was a prospective, multi-center, open-label, single-arm clinical trial to assess device safety and efficacy of the Cordella PA Sensor System in NYHA Class III Heart Failure patients compared to a Performance Goal (PG) of the rate of HF hospitalizations or all-cause mortality at 6 months based on a meta-analysis on the combined cohorts of CHAMPION-HF[7], CardioMEMS Post approval study[8], MEMS-HF[9], GUIDE-HF (NYHA Class III cohort)[3], and LAPTOP-HF[10] (control group only). This trial was conducted under the IDE# G190020. The patient population was composed of patients with a HF diagnosis of > 3 months with either preserved or reduced LVEF.

Subjects in this trial were categorized into three (3) different cohorts:

a. Cohort #1- Previously enrolled Control Arm subjects

- Upon change to single arm, subjects in this cohort were unblinded to their PAP measurements and informed about their previous group assignment and continued their Follow-up visit schedule.
- Additionally, subjects were asked, throughout the remaining Follow-up period, to complete a regular subject survey on their experience with PAP Measurements and PAP values.
- Upon change to single arm, clinicians were unblinded to PAP measurements and started managing the patients to target PA pressures per protocol/ CIP and according to Guideline Directed Medical Therapy (GDMT).
- Additionally, the clinical site was asked to contact the subject on a regular basis to discuss their PAP values.
- Separate subgroup analysis (safety and effectiveness) were performed.

b. Cohort #2- Previously enrolled Treatment Arm subjects

- As of month 12, subjects in this cohort were able to see their own PAP measurements for the remaining duration of the study.
- Clinicians continued to manage the patients to target PA pressures per protocol/CIP and according to GDMT.
- All primary and secondary safety and effectiveness analyses were performed.

c. Cohort #3- Newly enrolled subjects

- Subjects participated in the Screening/ Enrollment Visit, Cordella PA Sensor Implant Visit, and Follow-Up Visits.
- Clinicians managed the patients to target PA pressures per protocol/ CIP and according to GDMT.
- As of month 12, subjects in this cohort will be able to see their own PAP measurements for the remaining duration of the study.
- All primary and secondary safety and effectiveness analyses were performed.

The Cordella PA Sensor was implanted in conjunction with a right heart catheterization (RHC) procedure. During this visit, the Cordella PA Sensor, which is pre-mounted on a catheter Delivery System, was introduced via percutaneous venous access to the pulmonary artery. Once deployed, the Sensor PAP was calibrated using the Delivery System's fluid-filled catheter for independent reference measurements. The calibration coefficients for that Sensor/Reader/

Subject were stored in a database, allowing for consistent PAP calculations throughout the study duration. Also, at the Screening Visit, eligible subjects were provided with the commercially available Cordella HF System to measure BP, HR, SpO_2 and weight.

Subjects were observed until stable and discharged home with instructions to take their PAP measurements daily in addition to their weight, BP, HR and SpO_2, which were all wirelessly transmitted to a secure website for review using the myCordella Patient Management Portal.

Visibility to patients' daily data trends enabled the clinician to proactively manage the patients to target PA pressures per protocol and according to GDMT. The clinician contacted all subjects on a regular basis to discuss their health status and all patients were treated according to GDMT. All Subjects will return for follow up visits at 1, 6, 12, 18, 24 months, as well as at Year 3, 4 and 5, after the Cordella PA Sensor implant, or until study termination. The 3 month follow-up visit was performed as a remote/ virtual telemonitoring visit.

All subjects who received a Cordella PA Sensor Implant were followed for 6 months for the Primary Efficacy and Primary Safety Endpoints and will be followed for up to 5 years post implant. Additional monitoring of safety and efficacy assessments will be performed throughout the study duration, including evaluation of subject functional and health status, adverse events, Heart Failure (HF) related hospitalizations or equivalent (e.g., intravenous (IV) diuretics).

A total of 75 sites (71 US/4 EU) enrolled a subject in this trial. A subject is considered enrolled if the subject signed the consent form, completes the screening visit, and is reviewed by the Eligibility Committee. A subject is considered to be a screen failure if the subject signed the consent form but was subsequently determined ineligible based on the trial inclusion and/or exclusion criteria prior to implant.

The trial began in the USA with the first site for the trial initiated on November 8, 2019, and Enrollment into the trial started on January 10, 2020. After approval of protocol amendment V7.0 (November 21, 2021), the amendment not only increased the number of participating centers to one-hundred twenty (120) in the United States (US) and Europe (EU), as well as a change in trial design from a randomized to a single arm trial. After the approval of protocol amendment V7.0 (November 21, 2021) in December 2021 all sites were consequently converted to this single arm trial.

Enrollment was completed on March 8, 2023, and the last subject was implanted on March 31, 2023.

Out of the 738 enrolled subjects, 528 subjects received an implant **(Figure 9)**. Five-hundred twenty-eight (528) are a combination of 72 subjects in Cohort #1,

the previously enrolled Control Arm subjects; 88 subjects in Cohort #2, the previously enrolled Treatment Arm subjects; and 368 subjects in Cohort #3, the newly enrolled subjects. One-hundred twenty-five (125) subjects failed screening and 85 subjects were withdrawn prior to implant. Thirty-seven (37) subjects had an aborted implant.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the PROACTIVE- HF study was limited to patients who met the following inclusion criteria:

- Subject has given written informed consent
- Male or female, at least 18 years of age
- Diagnosis and treatment of HF (regardless of left ventricular ejection fraction (LVEF)) for ≥ 3 months and NYHA Class III HF at time of Screening
- Subjects should be on stable, optimally titrated medical therapy for at least 30 days, as recommended according to current American Heart Association (AHA)/American College of Cardiology (ACC) guidelines as standard-of-care for HF therapy in the United States, or current European Society of Cardiology (ESC) guidelines for HF treatment in Europe, with any intolerance documented
- Subjects who qualified for the following:
    1. HF related hospitalization in the past year i.e. one calendar day change
    2. HF treatment in a hospital day-care setting
    3. Or urgent outpatient clinic HF visit for IV diuretics within 12 month (last hospitalization should be 30 days before Screening /Enrollment)
    - Or N-terminal pro-Brain Natriuretic Peptide (NT-proBNP)) at time of Screening/ Enrollment defined as:
        - Subjects with LVEF ≤ 50%: NT-proBNP ≥ 1500 pg/mL.
        - Subjects with LVEF > 50%: NT-proBNP ≥ 800 pg/mL.

  Thresholds for NT-proBNP for both LVEF ≤ 50% and LVEF > 50%) will be corrected for body mass index (BMI) using a 4% reduction per BMI unit over 25 kg/m^2

- Subjects should be on diuretic therapy
- Subjects who are physically able to hold the Patient Reader unit (approximate weight 1.3lb) against the ventral thoracic surface for up to 2 minutes per day while in a seated position, as well as dock and undock the Patient Reader
- Subjects with sufficient eyesight, hearing, and mental capacity to respond to the Patient Reader's audio/visual cues and operate the Patient Reader
- Subject has sufficient Cellular and/ or Wi- Fi Internet coverage at home
- Subject agrees to return to the treating Investigator for all scheduled follow up

visits and can return to the hospital for follow up

Patients were not permitted to enroll in the PROACTIVE-HF study if they met any of the following exclusion criteria:

- Intolerance to all neuro-hormonal antagonists (i.e., intolerance to ACE-I, ARB, ARNI, and beta-blockers) due to hypotension or renal dysfunction
- ACC/AHA Stage D refractory HF (including having received or currently receiving pharmacologic circulatory support with inotropes)
- Subjects with history of recurrent pulmonary embolism (≥ 2 episodes within 5 years prior to Screening Visit) and/or deep vein thrombosis within 3 months of the Screening Visit
- Subjects who have had a major CV event (e.g., myocardial infarction, stroke) within 3 months of the Screening Visit
- Unrepaired severe valvular disease
- Subjects with significant congenital heart disease that has not been repaired and would prevent implantation of the Cordella PA Sensor or mechanical/tissue right heart valve(s)
- Subjects with known coagulation disorders
- Subjects with a hypersensitivity or allergy to platelet aggregation inhibitors including aspirin, clopidogrel, prasugrel, and ticagrelor; or patients unable to take dual antiplatelet or anticoagulants for one- month post implant
- Known history of life threatening allergy to contrast dye.
- Subjects whereby RHC is contraindicated
- Subjects with an active infection at the Sensor Implant Visit
- Subjects with a GFR <25 ml/min or who are on chronic renal dialysis
- Implanted with CRT-P or CRT-D for less than 90 days prior to screening visit
- Received or are likely to receive an advanced therapy (e.g., mechanical circulatory support or lung or heart transplant) in the next 12 months
- Subjects who are pregnant or breastfeeding
- Subjects who are unwilling or deemed by the Investigator to be unwilling to comply with the study protocol, or subjects with a history of non-compliance
- Severe illness, other than heart disease, which would limit survival to <1 year
- Subjects whose clinical condition, in the opinion of the Investigator, makes them an unsuitable candidate for the study
- Subjects enrolled in another investigational trial with an active Treatment Arm
- Subject who is in custody by order of an authority or a court of law

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 1, 6, 12, 18, 24 months, as well as at Year 3, 4 and 5, after the Cordella PA Sensor implant, or until study termination. Adverse events and complications were recorded at all visits. The key timepoints and assessments are shown in **Table 5**:

Table 5. PROACTIVE-HF / ETX-HFS-PA-03: Study Visit Schedule

Assessment	V1: Screening/ Enrollment (30 days)[15]	V2: Cordella PA Sensor Implant Visit	V3: Month 1 (±7 days)	V4 [11]: Month 3 (±7 days)	V5: Month 6 (±14 days)	V6: Month 12 (±30 days)	V7 to V8: Months 18, 24 (±30 days)	V9 to V11 Year 3, 4, 5 (±30 days)
Informed Consent	X							
Subject Demographics	X							
Study Eligibility Review and Committee Approval	X							
Cardiac/Medical & Surgical History	X							
Physical Exam, height, weight, and vital signs [1, 5]	X	X	X[12]		X	X	X	X
12-Lead ECG with Interpretation	X				X	X	X[4]	X
Urinalysis [2]	X							
Safety Labs (Chemistry/Hematology/ aPTT/ INR)	X				X	X	X[4]	X
Serum NT-pro BNP	X		X	X[12]	X	X	X	X
aPTT/ INR (if indicated)								
Echocardiogram [3]	X					X		X
Subject Training: Cordella™ HF System [14]	X							
Subject Training: CorPASS		X						
Cordella™ PA Sensor Implant		X						
Cordella System Use (daily)	X	X	X	X	X	X	X	X
Cordella™ PAP – dia/sys/mean/pulse		X[9]	X[5,6]	X[5,6]	X[5,6]	X[5,6]	X[5,6]	X[6]
RHC PAP / RAP/ PCWP/ CO/ CI/ RVP[8]		X						X[17]
Subject Status	X		X	X	X[10]	X[10]	X	X
6- Minute Walk Test	X				X	X[7]	X[4,7]	X[7]
NYHA Functional Classification	X[16]		X	X	X	X	X	X
KCCQ Quality of Life Questionnaires [5]	X		X	X	X	X	X	X
Concurrent/Cardiac Medications	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X
Health Economic Questionnaire							X[4]	
Subject Survey (optional)/ **Cohort #1 only[13]**	1. Month 1 after Unblinding 2. Quarterly until V11 / Year 5							
Site Survey (optional)/ **Cohort #1 only[13]**	1. Month 1 after Unblinding 2. Quarterly until V11 / Year 5							

1. Full Physical Examination and Height performed at Screening Visit only 2. Urine (V1) pregnancy test for females 3. Echo may be obtained within 3 or 6 months of Screening details are in section 8.1.10 4. At Month 24 only 5. via myCordella™ Patient App at home prior to visit. Baseline KCCQ will be completed on myCordella tablet following Cordella System distribution at Screening Visit 6. via myCordella™ Patient App seated and supine 7. Additional PAP Measurements will be obtained before and after 6-minute walk test 8. Additional RHC as needed for Re-calibration purposes at the clinician's discretion	9. Via CalEQ 10. Incl. question on assigned treatment at Visit 5 and 6 11. Visit should be completed remote/ virtually 12. If available 13. After subject gets unblinded to PAP Pressures at V6 or cross-over whatever comes first 14. Subject training on and distribution of the commercial Cordella™ System (should occur at Screening Visit (Visit 1). 15. Some study procedures need to be repeated in case a subject is implanted >30 days after Visit 1, details are in section 8.3.1. 16. may be obtained within the 30 day Study Visit 1 window 17. At V9/ Year 3 only

3. Clinical Endpoints

With regards to safety, the study had primary and secondary safety endpoints which are discussed below:

Primary Safety Endpoints:

- Freedom from device or system-related complications (DSRC) at 6 months will be tested against the null rate of 90%. Based on a one sample test of a proportion, a sample size of 450 patients provides greater than 95% power assuming a population rate of 95% based on a two-sided Type I error rate of 5%.
- Freedom from pressure sensor failure at 6 months will be tested against a null rate of 95%

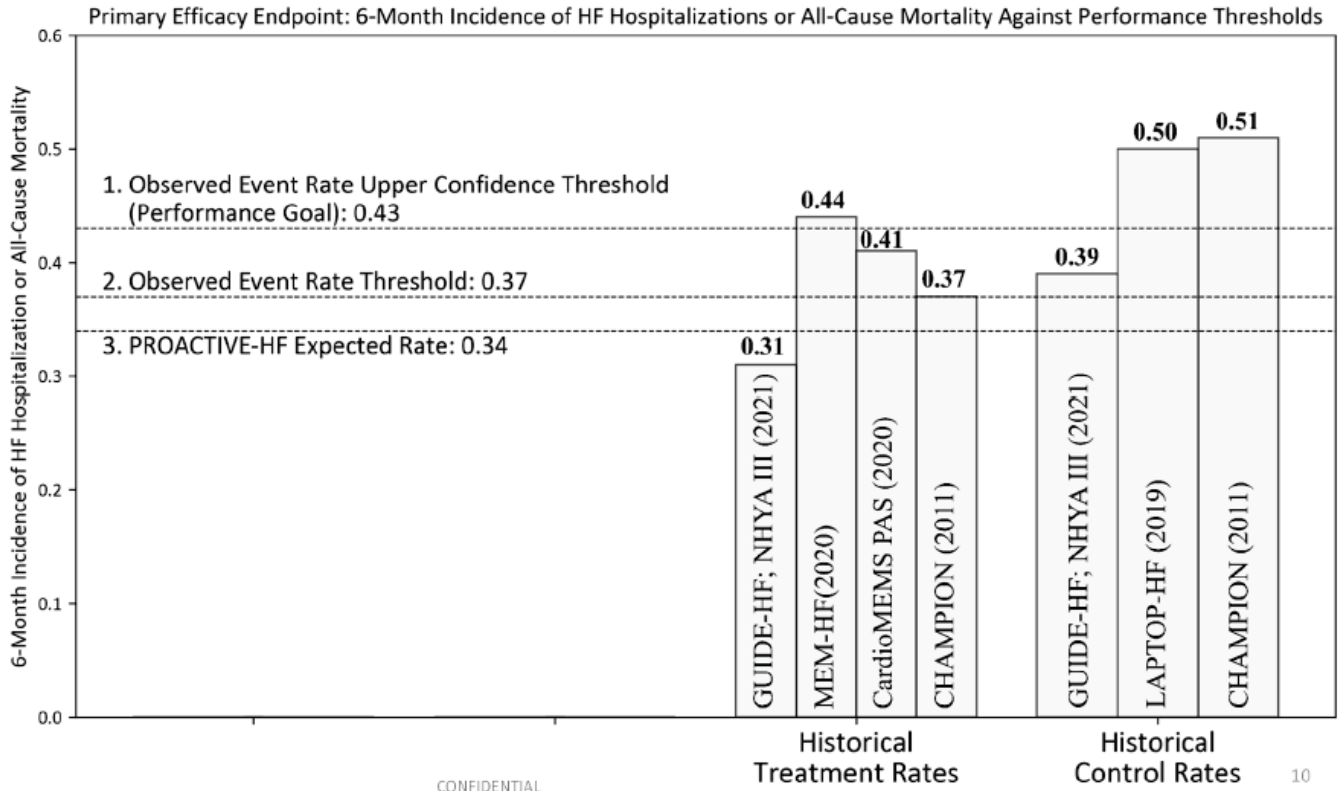
Secondary Safety Endpoints:

- Frequency of serious adverse events (SAEs) throughout the study
- Frequency of implant procedure and procedure related adverse events
- Pressure sensor failure rate throughout the study

With regards to effectiveness, the study had primary and secondary efficacy endpoints which are discussed below.

With regard to success/failure criteria, results of individual CardioMEMS studies and an internally derived meta-analysis were considered in determining the Primary Endpoint Performance Goal (PG) for the re-designed study. The meta-analysis was performed on the combined cohorts of CHAMPION-HF[7], CardioMEMS Post approval study[8], MEMS-HF[9], GUIDE-HF (NYHA Class III cohort)[3], and LAPTOP-HF[10] (control group only) as shown in Figure 10.

Figure 10: Results of Individual CardioMEMS Studies and Meta Analysis for Determining the Primary Endpoint Performance Goal



To meet the new objectives of the study, observed event rates in the single-arm PROACTIVE-HF should be similar to observed event rates in the treatment arm of CardioMEMS studies and lower than observed event rates in the control arm of CardioMEMS studies. Therefore, we set the PG below the meta-analysis upper bound 95% confidence interval of CardioMEMS treated patients, and below the meta-analysis estimates of CardioMEMS control patients and adjusted the goal downwards to account for a potential impact of treatment with SGLT2i. Furthermore, we also require that the single-arm PROACTIVE-HF observed event rate be lower than both the meta-analysis estimate of CardioMEMS treatment patients, and the lowest observed event rates of CardioMEMS control patients, further adjusted down by potential impact of SGLT2i.

Primary Efficacy Endpoint:

The primary endpoint was the 6-month incidence of HF related hospitalizations (HFH) or all-cause mortality.

For the primary endpoint of HFH and all-cause mortality at 6 months, the PG is 0.43 events per patient 6-month and, for study success, the upper confidence bound of the observed event rate for the planned study must be less than the PG. Additionally, the observed event rate must be lower than 0.37 events per patient 6-month.

Evaluating the upper bound of the confidence interval for the rate, ensures:

- the observed rate will be comparable to prior studies of active treatment (highest observed value = 0.44),
- the observed rate will be less than the mean rate from meta- analysis of prior studies of treatment and control, and
- the observed rate will be less than the lowest rate observed in the control studies (GUIDE-HF). The added requirement for the observed rate to be less than 0.37 provides further assurance that results are comparable to studies of prior treatment.

Based on this, the study will implant 450 subjects (single arm cohorts) leading to an expected evaluable cohort of 406 subjects. With a PG of 0.43 and a one-sided 0.025 alpha level, the study will have greater than 80% power assuming a population treatment rate of 0.34.

Secondary Efficacy Endpoints:

- The first secondary efficacy endpoint is incidence of HF Hospitalizations or all-cause mortality at 12 months compared to a PG. The PG of 0.70 for the first secondary efficacy endpoint of 12-month incidence of HFH or all-cause mortality was derived from clinically relevant, contemporary studies of NYHA class III HF subjects. Additionally, we require the observed event rate to be less than 0.59.
- Number of HFH at 6 and 12 months post-implant compared to the number of HFH in the 6 and 12 months prior to implant
- Comparison of the number of HFH or emergency department / hospital outpatient IV diuretic visits of Cohort #1 and Cohort #2 at 6 and 12 months post-implant
- Change of NT-pro BNP from baseline through 6 and 12 months
- Combined outcome of:
  - First and recurrent HFH
  - Emergency department / hospital outpatient IV diuretic visits
  - All-cause mortality

  At 6 months, added together with equal weighting into a total number of events
- HFH or emergency department / hospital outpatient IV diuretic visits at 6 and 12 months
- Cardiac and all-cause mortality
- Days alive and out of the hospital (DAOH)
- IV diuretic visits
- Heart failure related medication changes
- Change in PAP:
  a. From baseline through 6 and 12 months in subjects with a baseline mean PAP
     i. Above target range
     ii. Within or below target range
     iii. Overall
  b. Before and after 6-minute walk test (6MWT)

- Percentage of device success as documented by ability of the system to successfully transmit PAP data
- Patient outcome measures, measured by KCCQ
- Functional status improvement, as measured by NYHA and 6MWT
- Health economic analysis

B. Accountability of PMA Cohort

At the time of database lock, 738 patients had enrolled in the PROACTIVE-HF study (85.5% of screened patients) and a total of 528 patients (71.5% of enrolled patients) implanted with the device are available for analysis at the completion of the study on 29 September 2023. Implanted subjects were included in either the randomized Control Arm prior to the trial redesign (Cohort #1, N = 72 subjects), in the randomized Treatment Arm prior to the trial redesign (Cohort # 2, N=88 subjects), or in the Treatment Arm after the trial redesign (Cohort #3, N=368 subjects). Subjects in Cohorts #2 and #3 (N = 456) contribute to the primary safety and efficacy endpoints in PROACTIVE-HF. Subjects in Cohort #1 contribute to a substudy examining patient engagement with pulmonary artery pressures.

1. *Intent-to-Treat Population (ITT)*, includes all enrolled subjects intended to receive the Cordella PA Sensor who entered the Cath Lab, including those in whom Implant Procedure was not completed for whatever reason (e.g., Cordella PA Sensor Implant could not be performed due to anatomical reasons) from Cohort #2 and #3. The ITT was used for all analyses of safety endpoints.
2. *Modified Intent-to-Treat Population (mITT)*, includes all implanted subjects form Cohort #2 and Cohort #3. All primary and secondary effectiveness analyses were performed on the mITT.
3. *Per Protocol Population (PP)*, includes all mITT subjects without any major protocol deviations. All primary and secondary safety and effectiveness analyses were performed in addition on PP population. If PP and mITT populations were identical, analysis was performed based on mITT only.
4. *Cohort #1*- Previously enrolled Control Arm subjects- Population, this subgroup includes all Cohort #1 (previously enrolled Control Arm) subjects and was reported separately for all endpoints.

The trial enrollment and subject population are presented below in **Figure 11**.

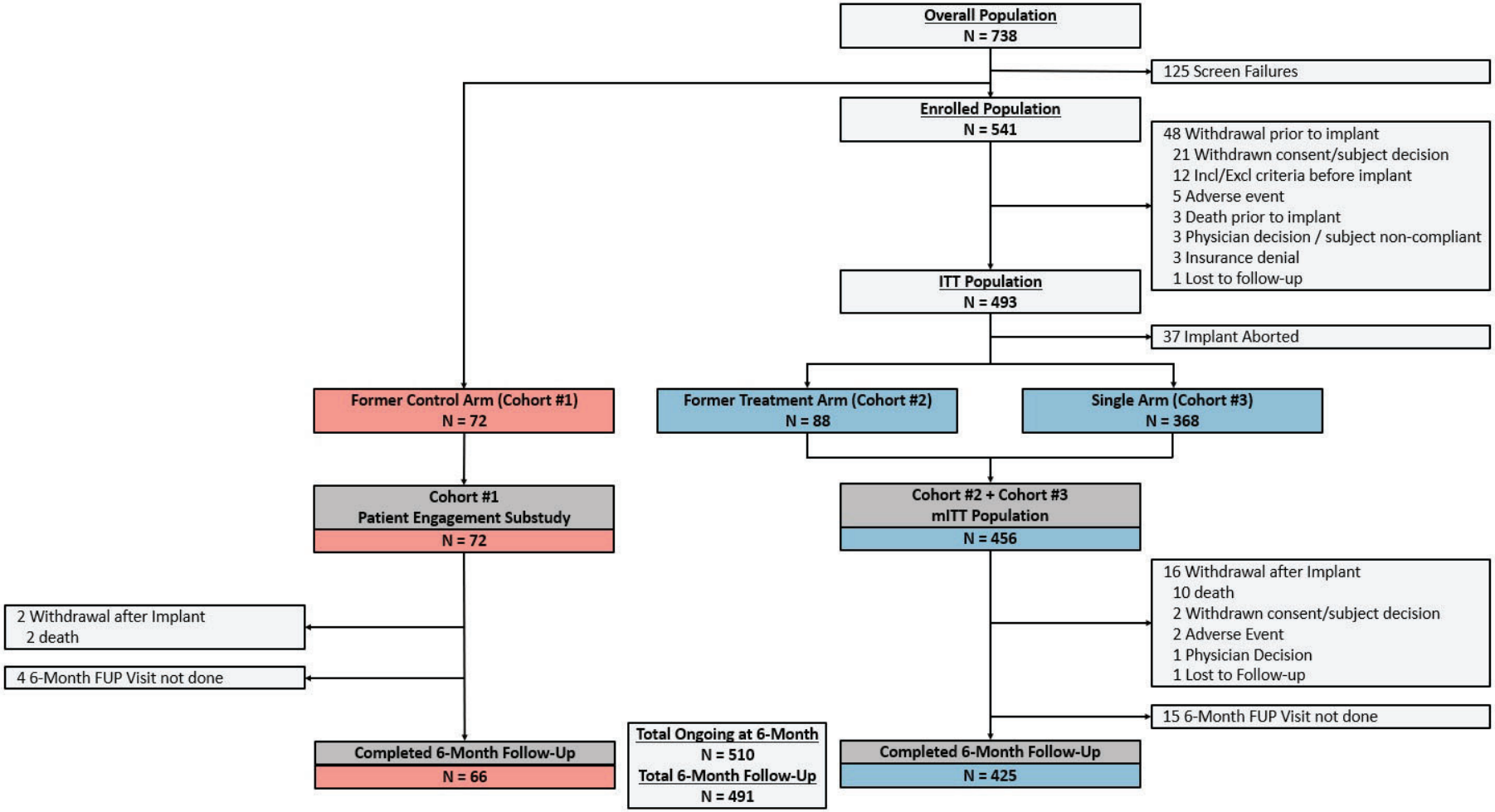


Figure 11: PROACTIVE-HF / ETX-HFS-PA-03: Patient Disposition

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a single arm study performed in the US.

Study Population and Baseline Parameters

mITT & mITT Stratified by Cohort Number

There were some differences between the cohorts as illustrated in the Table below, for example the proportion of patients in Cohort #3 on SGLT2i at baseline was greater than that of Cohort #1 (64.1% vs. 29.2%) and Cohort #2 (64.1% vs. 33.0%). Table 6 presents the demographics and patient characteristics by the mITT population and stratified by Cohort assignment.

Table 6. Demographics for mITT, Cohort #1, Cohort #2, and Cohort #3:

Characteristic	mITT (N=456)	Cohort #1 (N=72)	Cohort #2 (N=88)	Cohort #3 (N=368)
Demographics				
Age (years), Mean (SD)	63.5 (12.5)	65.9 (11.3)	64.5 (11.5)	63.3 (12.8)
Male, n (%)	276 (60.5%)	42 (58.3%)	56 (63.6%)	220 (59.8%)
Female, n (%)	180 (39.5%)	30 (41.7%)	32 (36.4%)	148 (40.2%)
Weight (kg), Mean (SD)	105.8 (25.8)	102.9 (22.8)	102.0 (23.3)	106.7 (26.4)
Height (cm), Mean (SD)	172.0 (10.6)	171.3 (11.3)	172.5 (9.9)	171.9 (10.8)
Body mass index (kg/m2), Mean (SD)	35.9 (8.8)	35.3 (8.4)	34.4 (7.8)	36.2 (9.0)
Race				
White, n (%)	347 (76.1%)	56 (77.8%)	68 (77.3%)	279 (75.8%)
Black, n (%)	84 (18.4%)	11 (15.3%)	14 (15.9%)	70 (19.0%)
Asian, n (%)	7 (1.5%)	0 (0%)	3 (3.4%)	4 (1.1%)
Hawaiian or Pacific Islander, n (%)	3 (0.7%)	1 (1.4%)	1 (1.1%)	2 (0.5%)
American Indian/Alaskan native, n (%)	2 (0.4%)	1 (1.4%)	1 (1.1%)	1 (0.3%)
Other, n (%)	4 (0.9%)	0 (0%)	0 (0%)	4 (1.1%)
Race not reported, n (%)	9 (2.0%)	3 (4.2%)	1 (1.1%)	8 (2.2%)
Ethnicity				
Hispanic or Latino, n (%)	20 (4.4%)	5 (6.9%)	3 (3.4%)	17 (4.6%)
Not Hispanic or Latino, n (%)	401 (87.9%)	61 (84.7%)	81 (92.0%)	320 (87.0%)
Ethnicity not reported, n (%)	13 (2.9%)	2 (2.8%)	0 (0%)	13 (3.5%)
Unknown, n (%)	22 (4.8%)	4 (5.6%)	4 (4.5%)	18 (4.9%)
Smoking History				
Never, n (%)	210 (46.1%)	34 (47.2%)	33 (37.5%)	177 (48.1%)
Previous, n (%)	209 (45.8%)	31 (43.1%)	43 (48.9%)	166 (45.1%)
Smoker, n (%)	37 (8.1%)	7 (9.7%)	12 (13.6%)	25 (6.8%)
Heart Failure Ejection Fraction				

Characteristic	mITT (N=456)	Cohort #1 (N=72)	Cohort #2 (N=88)	Cohort #3 (N=368)
LVEF ≤ 40% (HFrEF), n %	208 (45.6%)	33 (45.8%)	40 (45.5%)	168 (45.7%)
LVEF ≥ 50% (HFpEF), n %	201 (44.1%)	31 (43.1%)	37 (42.0%)	164 (44.6%)
40% < LVEF < 50% (HFmrEF), n (%)	45 (9.9%)	8 (11.1%)	10 (11.4%)	35 (9.5%)
Medical History/Surgical History				
Diabetes mellitus, n (%)	161 (35.3%)	26 (36.1%)	30 (34.1%)	131 (35.6%)
Chronic kidney disease, n (%)	198 (43.4%)	37 (51.4%)	32 (36.4%)	166 (45.1%)
Chronic obstructive pulmonary disease, n (%)	92 (20.2%)	15 (20.8%)	21 (23.9%)	71 (19.3%)
Coronary artery bypass graft, n (%)	81 (17.8%)	12 (16.7%)	15 (17.0%)	66 (17.9%)
Percutaneous coronary intervention, n (%)	134 (29.4%)	23 (31.9%)	28 (31.8%)	106 (28.8%)
Valve repair / replacement, n (%)	21 (4.6%)	5 (6.9%)	6 (6.8%)	15 (4.1%)
Heart Failure History				
Time since first diagnosis of HF [months], Mean (SD)	58.1 (68.4)	66.3 (62.5)	54.0 (59.0)	59.1 (70.5)
Time since first diagnosis of HF [months], Median	33.08	46.98	31.67	33.53
Time since first diagnosis of HF [months], Min	2.97	0.03	2.97	3.03
Time since first diagnosis of HF [months], Max	454.37	257.73	309.43	454.37
Etiology of Heart Failure				
Ischemic, n (%)	143 (31.4%)	26 (36.1%)	33 (37.5%)	110 (29.9%)
Non-Ischemic, n (%)	313 (68.6%)	46 (63.9%)	55 (62.5%)	258 (70.1%)
Number of HFH in prior year, Count (%)				
0	90 (19.7%)	7 (9.7%)	17 (19.3%)	73 (19.8%)
1	208 (45.6%)	48 (66.7%)	45 (51.1%)	163 (44.3%)
2	88 (19.3%)	9 (12.5%)	19 (21.6%)	69 (18.8%)
3	46 (10.1%)	5 (6.9%)	3 (3.4%)	43 (11.7%)
4	9 (2.0%)	1 (1.4%)	1 (1.1%)	8 (2.2%)
5	8 (1.8%)	2 (2.8%)	1 (1.1%)	7 (1.9%)
5+	7 (1.5%)	0 (0%)	2 (2.3%)	5 (1.4%)
Number of HFH in prior year, Mean (SD)	1.4 (1.3)	1.3 (1.0)	1.3 (1.2)	1.4 (1.3)
Number of HFH in prior year, Min	0	0	0	0
Number of HFH in prior year, Max	8	5	6	8
Other Cardiovascular History				
Hypertension, n (%)	403 (88.4%)	65 (90.3%)	74 (84.1%)	329 (89.4%)
Coronary artery disease, n (%)	269 (59.0%)	45 (62.5%)	57 (64.8%)	212 (57.6%)
Myocardial infarction, n (%)	118 (25.9%)	16 (22.2%)	21 (23.9%)	97 (26.4%)
Atrial fibrillation, n (%)	236 (51.8%)	39 (54.2%)	43 (48.9%)	193 (52.4%)
Transient ischemic attack, n (%)	23 (5.0%)	4 (5.6%)	3 (3.4%)	20 (5.4%)
Stroke, n (%)	48 (10.5%)	7 (9.7%)	7 (8.0%)	41 (11.1%)

Characteristic	mITT (N=456)	Cohort #1 (N=72)	Cohort #2 (N=88)	Cohort #3 (N=368)
Peripheral vascular disease, n (%)	61 (13.4%)	14 (19.4%)	10 (11.4%)	51 (13.9%)
Carotid artery disease, n (%)	33 (7.2%)	8 (11.1%)	4 (4.5%)	29 (7.9%)
Ventricular tachycardia, n (%)	88 (19.3%)	16 (22.2%)	19 (21.6%)	69 (18.8%)
Ventricular fibrillation, n (%)	18 (3.9%)	2 (2.8%)	4 (4.5%)	14 (3.8%)
Atrial flutter, n (%)	58 (12.7%)	9 (12.5%)	9 (10.2%)	49 (13.3%)
Implantable cardioverter defibrillator, n (%)	160 (35.1%)	21 (29.2%)	36 (40.9%)	124 (33.7%)
Cardiac resynchronization therapy, n (%)	82 (18.0%)	15 (20.8%)	15 (17.0%)	67 (18.2%)
Laboratory				
Estimated glomerular filtration rate [mL/min/1.73m2], Mean (SD)	54.7 (18.7)	50.1 (19.7)	54.3 (18.2)	54.8 (18.8)
NT-proBNP [pg/mL], Mean (SD)	1731.4 (3012.8)	1768.8 (3809.4)	2061.0 (4401.6)	1655.1 (2590.4)
Hemodynamics (Right Heart Catheterization)				
Systolic pulmonary artery pressure (mmHg), Mean (SD)	43.3 (14.9)	40.9 (13.0)	43.9 (16.4)	43.2 (14.6)
Diastolic pulmonary artery pressure (mmHg), Mean (SD)	18.8 (7.9)	18.4 (6.4)	19.6 (8.9)	18.6 (7.7)
Mean pulmonary artery pressure (mmHg), Mean (SD)	28.2 (10.1)	26.7 (8.9)	29.1 (11.6)	28.0 (9.7)
Right atrial pressure (mmHg), Mean (SD)	9.7 (6.7)	9.0 (4.6)	10.1 (5.7)	9.6 (7.0)
Pulmonary capillary wedge pressure (mmHg), Mean (SD)	16.5 (8.7)	15.3 (6.8)	16.9 (9.9)	16.4 (8.3)
Cardiac output (L/min), Mean (SD)	5.3 (3.2)	5.6 (3.3)	5.0 (1.3)	5.4 (3.5)
Cardiac index (L/min/m2), Mean (SD)	2.4 (0.6)	2.7 (1.4)	2.3 (0.5)	2.4 (0.6)
Vital Signs				
Systolic blood pressure, Mean (SD)	121.8 (19.1)	116.6 (18.7)	120.6 (17.6)	122.0 (19.5)
Diastolic blood pressure, Mean (SD)	72.9 (12.6)	67.9 (11.3)	72.7 (11.8)	73.0 (12.8)
Heart rate, Mean (SD)	77.2 (14.1)	77.7 (14.1)	77.6 (14.4)	77.1 (14.1)
Blood oxygen saturation, Mean (SD)	95.8 (2.8)	96.1 (2.5)	95.9 (2.9)	95.8 (2.8)
Heart Failure Medications				
Agents acting on the renin-angiotensin system, n (%)	310 (68.0%)	47 (65.3%)	61 (69.3%)	249 (67.7%)
Angiotensin receptor-neprilysin inhibitor, n (%)	199 (43.6%)	23 (31.9%)	36 (40.9%)	163 (44.3%)
Angiotensin II receptor blocker, n (%)	84 (18.4%)	21 (29.2%)	16 (18.2%)	68 (18.5%)
Angiotensin-converting enzyme inhibitor, n (%)	32 (7.0%)	4 (5.6%)	12 (13.6%)	20 (5.4%)
Beta blocker, n (%)	395 (86.6%)	61 (84.7%)	75 (85.2%)	320 (87.0%)
Diuretic, n (%)	454 (99.6%)	72 (100.0%)	88 (100.0%)	366 (99.5%)
Loop diuretic, n (%)	444 (97.4%)	72 (100.0%)	85 (96.6%)	359 (97.6%)
Thiazide diuretic, n (%)	2 (0.4%)	2 (2.8%)	2 (2.3%)	0 (0%)
Aldosterone antagonist, n (%)	310 (68.0%)	47 (65.3%)	54 (61.4%)	256 (69.6%)

Characteristic	mITT (N=456)	Cohort #1 (N=72)	Cohort #2 (N=88)	Cohort #3 (N=368)
Sodium-glucose transport protein 2 inhibitor, n (%)	265 (58.1%)	21 (29.2%)	29 (33.0%)	236 (64.1%)
Hydralazine, n (%)	35 (7.7%)	5 (6.9%)	6 (6.8%)	29 (7.9%)
Nitrates, n (%)	83 (18.2%)	12 (16.7%)	13 (14.8%)	70 (19.0%)
Functional Capacity & Quality of Life				
New York heart association functional class III, n (%)	456 (100.0%)	71 (98.6%)	88 (100.0%)	367 (99.7%)
Kansas City cardiomyopathy questionnaire overall summary score (points), Mean (SD)	52.8 (22.8)	49.7 (23.8)	52.4 (22.7)	52.8 (22.9)
Six-minute walk test (m), Mean (SD)	259.5 (121.1)	281.5 (133.6)	270.7 (120.7)	256.9 (121.2)
Enrollment Type				
Enrollment Type: HFH, n (%)	150 (32.9%)	31 (43.1%)	37 (42.0%)	113 (30.7%)
Enrollment Type: NT-proBNP, n (%)	89 (19.5%)	6 (8.3%)	16 (18.2%)	73 (19.8%)
Enrollment Type: HFH and NT-proBNP, n (%)	216 (47.4%)	34 (47.2%)	34 (38.6%)	182 (49.5%)
Enrollment Type: Does Not Meet Criteria, n (%)	1 (0.2%)	1 (1.4%)	1 (1.1%)	0 (0%)

LVEF = Left Ventricular Ejection Fraction, HF = Heart Failure, HFH = Heart Failure Hospitalization; NT-proBNP = N-Terminal Prohormone of Brain Natriuretic Peptide

D. Safety and Effectiveness Results

1. Safety Results

Primary Safety Results

Primary Safety Endpoints: Main Analysis

The analysis of safety was based on the Intention to Treat population (ITT) from Cohort #2 and Cohort #3, comprising 493 patients available for the 6-month evaluation. The key safety outcomes for this study are presented below in Tables 7 to 9. Adverse effects are reported in Tables 10 to 11.

First Primary Safety Endpoint

The first primary safety endpoint describes freedom from a Device/System Related Complications (DSRC) through 6 months and was tested against the null rate of 90%. In the ITT population a total of four (4) DSRCs occurred. The probability of being free from a DSRC at 6 months post implant procedure was 99.2% [95% CI: 97.9%, 99.7%]. The lower bound of the confidence interval, based on the Kaplan-Meier (KM) method, is higher than the null rate of 90%. (**Table 7** and KM plot **Figure 12**).

The first primary safety endpoint was met.

None of the DSRCs resulted in permanent subject impairment or death and all subjects recovered without sequelae. Clinical details of all DSRCs (four (4) events in ITT and one (1) event in Cohort#1) are shown in **Table 8.**

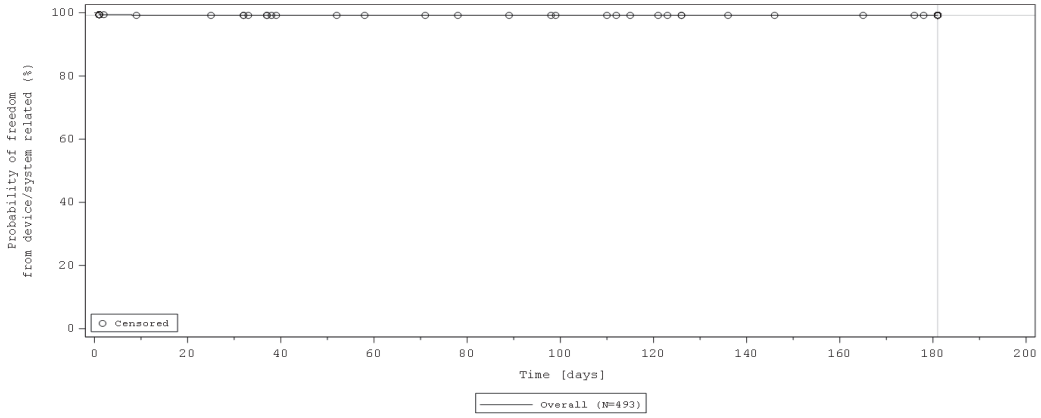
Table 7: PROACTIVE-HF / ETX-HFS-PA-03: Freedom From Device / System Related Complications – Results Through 6 months for ITT Population

Item	Result	ITT (N=493)
Subject with any DSRC	n (%)	4 (0.8%)
Censored	n (%)	489 (99.2%)
Subjects completed 6 months and without any DSRC	n (%)	439 (89.0%)
Subjects withdrew prior to 6 months and without any DSRC	n (%)	50 (10.1%)
Time to first DSRC (days) **		
25% percentile [95% CI]	181.0	
Median [95% CI]	181.0	
75% percentile [95% CI]	181.0	
Minimum	0.0	
Maximum	181.0	
Probability of being free from DSRC	**rate [95% CI]**	99.2 [97.9 – 99.7]

** With a very small proportion of subjects who have experienced an event, the median time is likely to be shorter than the actual time to event in the population; based on the limited number of events observed there is an underestimate of the true underlying time to event.

Probability of being free from DSRC at 6 months was estimated using the Kaplan-Meier method.

Figure 12: First Primary Safety Endpoint Analysis: Freedom From Device / System Related Complications Kaplan-Meier Plot



* Circles: In case of event, time to event = [(Date of event – date of Implant visit) + 1]; In case of no event, time to event = [(Date of last available date – date of Implant visit) + 1], this data will be censored.

Table 8: Summary of DSRCs as Adjudicated by the CEC (ITT Population and Cohort #1)

Event Description and Term	N (%)	Outcome
Further Migration of the Cordella Sensor / Device Dislocation	1 (0.2%)	Recovered
Right internal jugular blood vessel complications secondary to device insertion attempt / Procedure Complication	1 (0.2%)	Recovered
Implant Device Complication/ Complication associated with device	1 (0.2%)	Recovered
Device breakage/ Pressure sensor fracture	1 (0.2%)	Recovered
Total Subjects Experiencing a DSRC in ITT population	4 (0.8%)	
Event Description and Term	**N (%)**	**Outcome**
LV-Lead dislodgement/ Lead Dislodgement	1 (1.4%)	Recovered
Total Subjects Experiencing a DSRC in Cohort #1	1 (1.4%)	

Second Primary Safety Endpoint

The second primary safety endpoint describes freedom from Pressure Sensor Failure (PSF) through 6 Months, which was tested against the null rate of 95%. With one (1) event the Freedom from Pressure Sensor Failure rate was 99.8% **(Table 9)**. The probability of being free from a Pressure Sensor Failure event at 6 months post implant procedure was 99.8 % [95% CI: 98.6%, 100%]. The lower bound of the confidence interval, based on the KM method (**Figure 13**), is higher than the null rate of 95%.

The second primary safety endpoint was met.

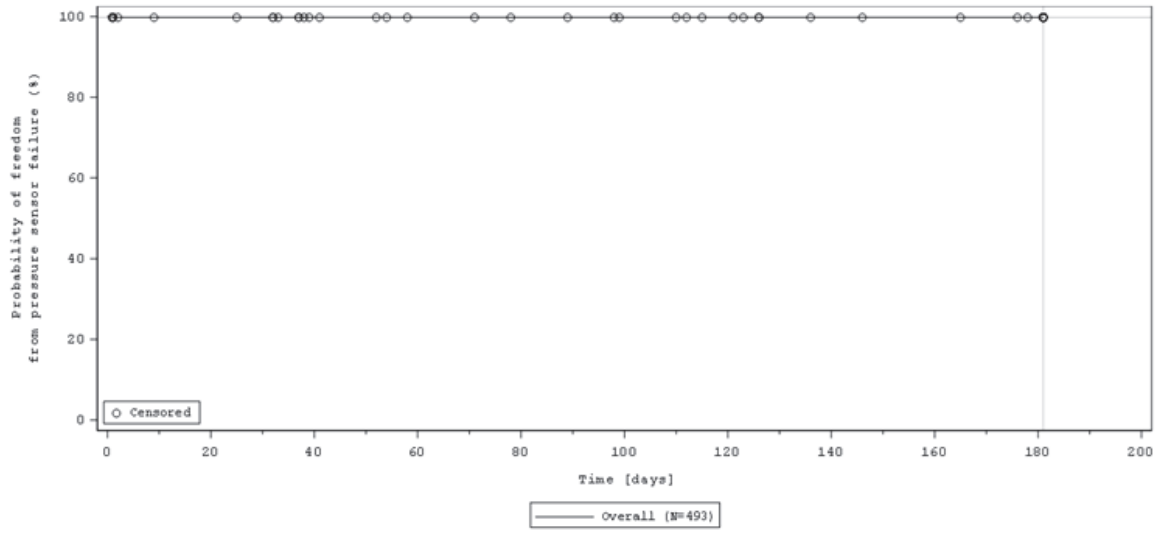
The event of PSF is ongoing with the device implanted and without any further related events.

Table 9: Second Primary Safety Endpoint Analysis: Freedom from Pressure Sensor Failure

Item	Result	ITT (N=493)
Subject with any PSF	**n (%)**	1 (0.2%)
Censored	**n (%)**	492 (99.8%)
Subjects completed 6 months and without any PSF	**n (%)**	440 (89.2%)
Subjects withdrew prior to 6 months and without any PSF	**n (%)**	52 (10.5%)
Time to first PSF (days)		
25% percentile [95% CI]		181.0
Median [95% CI]		181.0
75% percentile [95% CI]		181.0
Minimum		0.0
Maximum		181.0
Probability of being free from PSF	**rate [95% CI]**	0.998 [0.986 - 1.0]

Probability of being free from PSF at 6 months was estimated using the Kaplan-Meier method.

Figure 13: Second Primary Safety Endpoint Analysis: Freedom from Pressure Sensor Failure Kaplan-Meier Plot



* Circles: In case of event, time to event = [(Date of event – date of Implant visit) + 1]; In case of no event, time to event = [(Date of last available date – date of Implant visit) + 1], this data will be censored.

Secondary Safety Results

Secondary safety endpoints were based on mITT population for (1) Pressure Sensor Failure rate throughout the study, and ITT population for (2) frequency of site reported SAEs throughout the study and (3) frequency of CEC adjudicated implant procedure and procedure-related AEs and SAEs.

Pressure Sensor Failure Rate throughout the Study

Up to the 6-month FU visit only (1) Pressure Sensor Failure has been reported.

Frequency of Serious Adverse Events (SAEs) throughout the Study

Table 10 presents a summary of serious adverse events as reported by investigators. There were no unanticipated adverse device effects (UADEs).

Table 10: Predefined Serious Adverse Events by Category Through 6 Months for ITT and Cohort #1 Populations

Item	Result	ITT (N=493)	Cohort #1 (N=72)	ITT + Cohort 1 (N=565)	Cohort 1 vs ITT p-value
Subjects with at least one predefined SAE	n (%) n*	196 (39.8%) 425.0	31 (43.1%) 85.0	227 (40.2%) 510.0	0.5938
Heart Failure	n (%) n*	79 (16.0%) 100.0	16 (22.2%) 31.0	95 (16.8%) 131.0	0.189
ED Visit	n (%) n*	4 (0.8%) 4.0	0 (0%)	4 (0.7%) 4.0	0.4431
Hospitalization	n (%) n*	72 (14.6%) 90.0	16 (22.2%) 31.0	88 (15.6%) 121.0	0.0959
Urgent, Unscheduled Outpatient Office/ Practice	n (%) n*	2 (0.4%) 2.0	0 (0%)	2 (0.4%) 2.0	0.5882
Acute Kidney Injury (AKIN)	n (%) n*	22 (4.5%) 26.0	7 (9.7%) 8.0	29 (5.1%) 34.0	0.0589
Bleeding	n (%) n*	6 (1.2%) 6.0	4 (5.6%) 4.0	10 (1.8%) 10.0	0.0091
Conduction Disturbances and Arrhythmias	n (%) n*	28 (5.7%) 35.0	4 (5.6%) 4.0	32 (5.7%) 39.0	0.9661
Hemoptysis	n (%) n*	12 (2.4%) 13.0	1 (1.4%) 1.0	13 (2.3%) 14.0	0.5806
Myocardial Infarction (MI)	n (%) n*	3 (0.6%) 3.0	1 (1.4%) 1.0	4 (0.7%) 4.0	0.4607
Pulmonary Embolism	n (%) n*	6 (1.2%) 7.0	0 (0%)	6 (1.1%) 7.0	0.3467
Pulmonary Occlusion	n (%) n*	0 (0%)	0 (0%)	0 (0%)	NE
Renal Dysfunction	n (%) n*	8 (1.6%) 9.0	1 (1.4%) 1.0	9 (1.6%) 10.0	0.8823
Stroke and Trans Ischemic Attach (TIA)	n (%) n*	0 (0%)	1 (1.4%) 1.0	1 (0.2%) 1.0	0.0088
Vascular Access Site and Access-Related Complications	n (%) n*	4 (0.8%) 4.0	2 (2.8%) 2.0	6 (1.1%) 6.0	0.1284
Vessel Trauma	n (%) n*	4 (0.8%) 4.0	0 (0%)	4 (0.7%) 4.0	0.4431
Other	n (%) n*	123 (24.9%) 215.0	17 (23.6%) 30.0	140 (24.8%) 245.0	0.8059
Item	**Result**	**ITT (N=493)**	**Cohort #1 (N=72)**	**ITT + Cohort 1 (N=565)**	**Cohort 1 vs ITT p-value**
Subjects with at least one OTHER SAE	n (%) n*	123 (24.9%) 215.0	17 (23.6%) 30.0	140 (24.8%) 245.0	0.8059
Blood and lymphatic system disorders	n (%) n*	4 (0.8%) 6.0	0 (0%)	4 (0.7%) 6.0	0.4431
Cardiac disorders	n (%) n*	6 (1.2%) 7.0	1 (1.4%) 2.0	7 (1.2%) 9.0	0.902
Ear and labyrinth disorders	n (%) n*	1 (0.2%) 1.0	0 (0%)	1 (0.2%) 1.0	0.7021
Gastrointestinal disorders	n (%) n*	12 (2.4%) 14.0	1 (1.4%) 1.0	13 (2.3%) 15.0	0.5806
General disorders and administration site conditions	n (%) n*	8 (1.6%) 9.0	2 (2.8%) 4.0	10 (1.8%) 13.0	0.4875
Hepatobiliary disorders	n (%) n*	6 (1.2%) 7.0	0 (0%)	6 (1.1%) 7.0	0.3467
Immune system disorders	n (%) n*	1 (0.2%) 1.0	0 (0%)	1 (0.2%) 1.0	0.7021
Infections and infestations	n (%) n*	46 (9.3%) 63.0	9 (12.5%) 11.0	55 (9.7%) 74.0	0.3967
Injury, poisoning and procedural complications	n (%) n*	10 (2.0%) 11.0	0 (0%)	10 (1.8%) 11.0	0.2227
Investigations	n (%) n*	2 (0.4%) 2.0	0 (0%)	2 (0.4%) 2.0	0.5882
Metabolism and nutrition disorders	n (%) n*	9 (1.8%) 9.0	3 (4.2%) 4.0	12 (2.1%) 13.0	0.1981
Musculoskeletal and connective tissue disorders	n (%) n*	4 (0.8%) 4.0	0 (0%)	4 (0.7%) 4.0	0.4431
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	n (%) n*	1 (0.2%) 1.0	0 (0%)	1 (0.2%) 1.0	0.7021
Nervous system disorders	n (%) n*	13 (2.6%) 16.0	1 (1.4%) 1.0	14 (2.5%) 17.0	0.5245
Product issues	n (%) n*	6 (1.2%) 6.0	2 (2.8%) 2.0	8 (1.4%) 8.0	0.2951
Psychiatric disorders	n (%) n*	2 (0.4%) 2.0	1 (1.4%) 1.0	3 (0.5%) 3.0	0.2836
Renal and urinary disorders	n (%) n*	2 (0.4%) 2.0	0 (0%)	2 (0.4%) 2.0	0.5882
Respiratory, thoracic and mediastinal disorders	n (%) n*	25 (5.1%) 32.0	3 (4.2%) 4.0	28 (5.0%) 36.0	0.7412
Skin and subcutaneous tissue disorders	n (%) n*	4 (0.8%) 4.0	0 (0%)	4 (0.7%) 4.0	0.4431
Surgical and medical procedures	n (%) n*	1 (0.2%) 1.0	0 (0%)	1 (0.2%) 1.0	0.7021
Vascular disorders	n (%) n*	16 (3.2%) 17.0	0 (0%)	16 (2.8%) 17.0	0.121
Item	**Result**	**ITT (N=493)**	**Cohort #1 (N=72)**	**ITT + Cohort 1 (N=565)**	**Cohort 1 vs ITT p-value**
Subjects with at least one Unanticipated SAE	n (%) n*	151 (30.6%) 297.0	24 (33.3%) 45.0	175 (31.0%) 342.0	0.6429
Blood and lymphatic system disorders	n (%) n*	4 (0.8%) 5.0	0 (0%)	4 (0.7%) 5.0	0.4431
Cardiac disorders	n (%) n*	59 (12.0%) 82.0	10 (13.9%) 13.0	69 (12.2%) 95.0	0.6419
Ear and labyrinth disorders	n (%) n*	1 (0.2%) 1.0	0 (0%)	1 (0.2%) 1.0	0.7021
Gastrointestinal disorders	n (%) n*	13 (2.6%) 14.0	2 (2.8%) 3.0	15 (2.7%) 17.0	0.9446
General disorders and administration site conditions	n (%) n*	7 (1.4%) 7.0	2 (2.8%) 4.0	9 (1.6%) 11.0	0.39
Hepatobiliary disorders	n (%) n*	4 (0.8%) 5.0	0 (0%)	4 (0.7%) 5.0	0.4431
Immune system disorders	n (%) n*	1 (0.2%) 1.0	0 (0%)	1 (0.2%) 1.0	0.7021
Infections and infestations	n (%) n*	41 (8.3%) 51.0	8 (11.1%) 9.0	49 (8.7%) 60.0	0.4312
Injury, poisoning and procedural complications	n (%) n*	12 (2.4%) 12.0	2 (2.8%) 2.0	14 (2.5%) 14.0	0.8609
Investigations	n (%) n*	1 (0.2%) 1.0	0 (0%)	1 (0.2%) 1.0	0.7021
Metabolism and nutrition disorders	n (%) n*	14 (2.8%) 15.0	2 (2.8%) 2.0	16 (2.8%) 17.0	0.9764
Musculoskeletal and connective tissue disorders	n (%) n*	3 (0.6%) 3.0	1 (1.4%) 1.0	4 (0.7%) 4.0	0.4607
Nervous system disorders	n (%) n*	11 (2.2%) 14.0	3 (4.2%) 3.0	14 (2.5%) 17.0	0.3237
Product issues	n (%) n*	3 (0.6%) 4.0	3 (4.2%) 3.0	6 (1.1%) 7.0	0.0059
Psychiatric disorders	n (%) n*	2 (0.4%) 2.0	1 (1.4%) 1.0	3 (0.5%) 3.0	0.2836
Renal and urinary disorders	n (%) n*	18 (3.7%) 23.0	2 (2.8%) 2.0	20 (3.5%) 25.0	0.7079
Respiratory, thoracic and mediastinal disorders	n (%) n*	30 (6.1%) 37.0	1 (1.4%) 1.0	31 (5.5%) 38.0	0.1021
Skin and subcutaneous tissue disorders	n (%) n*	4 (0.8%) 4.0	0 (0%)	4 (0.7%) 4.0	0.4431
Surgical and medical procedures	n (%) n*	2 (0.4%) 2.0	0 (0%)	2 (0.4%) 2.0	0.5882
Vascular disorders	n (%) n*	13 (2.6%) 14.0	1 (1.4%) 1.0	14 (2.5%) 15.0	0.5245

Of note, with an event rate of 3.0% for all-cause hemoptysis, the event rate of this safety endpoint in the early experience with this new device is numerically higher than prior studies completed to date with similar PAP-measuring devices, such as in CHAMPION (0.2%), GUIDE-HF (0.3%) and MONITOR-HF (2.3%).

Frequency of Implant Procedure and Procedure-Related Adverse Events and Serious Adverse Events

Table 11 presents a summary of CEC adjudicated implant procedure and/or Cordella PA Sensor System related AEs and SAEs.

Table 11: Summary of CEC adjudicated Non-DSRC related AEs or SAEs

Item	**Result** **n=Number of subjects (%)** **n*=Number of events**	**ITT (N=493)**
Subjects with at least one predefined AE or SAE with study device or implant procedure relationship	**n (%) n***	37* (7.5%) **39**
Bleeding	**n (%) n***	3 (0.6%) 3
Conduction Disturbances and Arrhythmias	**n (%) n***	4 (0.8%) 4
Heart Failure	**n (%) n***	2 (0.4%) 2
Hemoptysis	**n (%) n***	15 (3.0%) 16
Pulmonary Embolism	**n (%) n***	1 (0.2%) 1
Vascular Access Site and Access-Related Complications	**n (%) n***	12 (2.4%) 13
Other	**n (%) n***	16 (3.2%) **16**
TOTAL	**n (%) n***	**52 (10.5%) 54**
* Subjects may overlap in Predefined AE/SAE Categories and Category other		

2. Effectiveness Results

The analysis of effectiveness was based on the 456 evaluable patients at the sixth month time point. Key effectiveness outcomes are presented in Tables 12 to 14.

Primary Effectiveness Results

Primary Efficacy Endpoint: Main Analysis

The historical composite event rates of HF hospitalization and all-cause mortality obtained

from CardioMEMS literature and an internally derived meta-analysis for patients managed with PAP-guided HF management ranged from 0.31-0.44 events per patient 6-month and the historical composite event rates for the control arm patients ranged from 0.39-0.51.[3,7,8,9,10]

The primary endpoint was based on all mITT subjects. The 6-month incidence of HF related hospitalizations or all-cause mortality was 0.1589 [95% CI: 0.1200, 0.2106] events per patient 6-month. The observed rate of 0.1589 was significantly less than PG (0.1589 vs 0.43; p<0.0001). Given that the upper confidence bound of the observed event rate was less than PG (0.1589 vs 0.43), the observed rate was significantly lower than PG, and the observed rate was less than 0.37, all criteria for the primary efficacy were satisfied and the primary efficacy endpoint was met.

Of note, while the PROACTIVE-HF aimed to enroll NYHA class III HF patients, the final event rate for the primary effectiveness endpoint (0.1589) was numerically much lower than the average event rate derived from published results from clinically relevant, contemporary studies of NYHA class III HF subjects (as evidenced by an historical performance goal originally set at 0.43). While supportive of the overall benefit of the device, the benefit profile was not compared against concurrent standard of care subjects which should be taken into account when considering this device for a patient until additional data is available.

The primary efficacy endpoint summary statistics are shown in **Table 12**.

Table 12: Primary Endpoint Analysis and Components

Overall Primary Efficacy Endpoint Analysis and Components	**Result**	**mITT (N=456)**
6-month incidence of HF hospitalization or all-cause mortality	Event rate*	0.1589
	[95% CI]*	0.1200-0.2106
	p-value	<0.0001**
6-month incidence of HF hospitalization	Event Rate *	0.1334
	[95% CI]*	0.0989-0.1798
6-month incidence of all-cause mortality	Event Rate*	0.0221
	[95% CI]*	0.0119-0.0411
Number of HF hospitalization	n	60
Number of all-cause mortality	n	10
Total number of HF hospitalization or all-cause mortalities	n	70
HF hospitalization or all-cause mortalities subject event rate	n	456
	mean (SD)	0.1793 (0.5403)
	median	0.0
	min	0.0
	max	3.46
	missing (%)	0 (0%)
HF hospitalization or all-cause mortalities number of events per subject	n	456
	mean (SD)	0.15 (0.45)
	median	0.0

	min	0
	max	3
	missing (%)	0 (0%)
* Event rates with 95% confidence intervals were calculated using a negative binomial model **A one-sided p-value < 0.025 indicates that the 6 month incidence of HF hospitalizations or all-cause mortality < 0.43		
HF = Heart Failure Hospitalization, CI = Confidence Interval		

Primary Efficacy Endpoint: Stratified by Cohort Number

The main analysis was repeated on the individual cohort numbers and interpretation of p-values is done in a descriptive manner only. In the Cohort #1 population, the 6-month incidence of HF related hospitalizations or all-cause mortality was 0.3106 [95% CI: 0.1341, 0.7195] events per patient 6-month. The observed rate was not significantly less than PG (0.3106 vs 0.43; p=0.2214).

Comparison of the 6-month incidence of HF hospitalization or all-cause mortality event rates between subgroups was done with a negative binomial model. An alpha level of 0.15 is used for subgroup comparisons to balance type I and II error concerns given the study is not prospectively powered for such statistical hypothesis tests. The subgroup comparisons are generally considered to be exploratory and hypothesis generating. There is no adjustment for multiple comparisons.

The 6-month incidence of HF related hospitalizations or all-cause mortality was significantly different between Cohort #1 and the mITT population (Cohort #2 plus Cohort #3) (0.3106 vs. 0.1589, p=0.0858). Differences between Cohort #2 and Cohort #3 event rates (0.1557 vs. 0.1595, p=0.8979) were not significant. The primary efficacy endpoint summary statistics for Cohort #1, Cohort #2, and Cohort #3 are shown in **Table 13**.

Table 13: Primary Endpoint Analysis and Components Stratified by Cohort Number

Efficacy Endpoint Analysis and Components	Result	Cohort #1 (N=72)	Cohort #2 (N=88)	Cohort #3 (N=368)
6-month incidence of HF hospitalization or all-cause mortality	Event rate*	0.3106	0.1557	0.1595
	[95% CI]*	0.1341-0.7195	0.0731-0.3313	0.1180-0.2156
	p-value	0.2214	0.0042**	<0.0001**
6-month incidence of HF hospitalization	Event Rate*	0.269	0.1279	0.1347
	[95% CI]*	0.1234-0.5867	0.0590-0.2770	0.0975-0.1861

6-month incidence of all-cause mortality	Event Rate*	0.0279	0.023	0.0219
	[95% CI]*	0.0070-0.1114	0.0057-0.0919	0.0110-0.0438
Number of HF hospitalization	n	18	11	49
Number of all-cause mortality	n	2	2	8
Total number of HF hospitalization or all-cause mortalities	n	20	13	57
HF hospitalization or all-cause mortalities subject event rate	n	72	88	368
	mean (SD)	0.3351 (1.1326)	0.1643 (0.5516)	0.1829 (0.5383)
	median	0	0	0
	min	0	0	0
	max	6.84	3.03	3.46
	missing (%)	0 (0%)	0 (0%)	0 (0%)
HF hospitalization or all-cause mortalities number of events per subject	n	72	88	368
	mean (SD)	0.28 (0.86)	0.15 (0.49)	0.15 (0.44)
	median	0	0	0
	min	0	0	0
	max	5	3	3
	missing (%)	0 (0%)	0 (0%)	0 (0%)
Cohort #1 vs. mITT (Cohort #2 & Cohort #3) Event Rate p-value		0.0859†		
Cohort #1 vs. Cohort #2 Event Rate p-value		0.2378†		
Cohort #2 vs. Cohort #3 Event Rate p-value		0.8979†		
*Event rates with 95% confidence intervals were calculated using a negative binomial model **A one-sided p-value < 0.025 indicates that the 6 month incidence of HF hospitalizations or all-cause mortality < 0.43 † alpha =0.15 for subgroup comparisons				
HF = Heart Failure Hospitalization, CI = Confidence Interval				

Secondary Effectiveness Results

All secondary efficacy endpoints were based on the mITT population and are applicable to 6-month follow-up. Key secondary efficacy endpoints covered at 12-month follow-up include 1) the incidence of HF hospitalization and all-cause mortality at 12 months, 2) The number of HF hospitalizations at 12 months post-implant compared to the number of HF hospitalizations in the 12 months prior to implant, 3) Comparison of the number of HF Hospitalizations or Emergency Department/ Hospital Outpatient IV diuretic visits of Cohort #1 and Cohort #2 + Cohort #3 at 12 months post implant, 4) change of N-terminal pro B-type Natriuretic Peptide (NT-proBNP) from Baseline through 12 months, 5) heart failure hospitalization or HF Emergency Department / Hospital Outpatient IV diuretic visits at 12 months, and 6) Change in pulmonary artery pressure from baseline through 12 months. 6-month results are presented below.

- The number of HF hospitalizations per subject at 6 months post-implant was significantly fewer than the number of HF hospitalizations per subject in the 6 months prior to implant in the mITT (0.6 ± 0.7 vs 0.1 ± 0.4; $p<0.0001$).
- For every HF hospitalizations or emergency department /hospital outpatient IV diuretic visit event in Cohort #2 and Cohort #3 there were 1.4725 events in Cohort #1. The rate of events in Cohort #1 compared to the rate of events in Cohort #2 and Cohort #3 (0.2508 vs. 0.1703, p=0.0697) was significant (alpha level 0.15).
- Mean NT-proBNP decreased from Screening to 6 months, however the change was not significant (1731.4 ± 3012.8 vs. 1632.5 ± 2742.4 pg/ml, p=0.0628).
- In the mITT population, 63 (13.8%) subjects had at least one of the combined outcomes of first and recurrent HF hospitalization, emergency department / hospital outpatient IV diuretic visits, and all-cause mortality with an event rate of 0.1925 [95% CI: 0.156, 0.2375]. These were primarily made up of first and recurrent HF hospitalization (N=60, 84% of total events), followed by emergency department / hospital outpatient IV diuretic visits (N = 17, 19.5% of total events) and all-cause mortality (N=10, 11.5% of total events).
- In the mITT population, 56 (12.3%) subjects had at least one of the combined outcomes of HF hospitalization or HF emergency/ outpatient IV diuretic visits with an event rate of 0.1703 [95% CI: 0.1362, 0.213]. These were primarily made up of HF hospitalization (N=60, 78% of total events), followed by emergency department / hospital outpatient IV diuretic visits (N = 17, 22% of total events).
- In the mITT population, there were 10 all-cause deaths, 6 of which were cardiac related. All-cause mortality event rate was 0.0221 [95% CI: 0.0119, 0.0411] and cardiac mortality event rate was 0.0133 [95% CI: 0.006, 0.0295].
- Patients in the mITT population spent an average 172.0 ± 27.2 days alive and out of hospital.
- In the mITT population, 14 (3.1%) subjects had 17 outpatient IV diuretic visits with an event rate of 0.0376 [95% CI: 0.0234, 0.0605]. These were primarily made of hospital outpatient IV diuretic visits (N=10, 59% of total events) followed by HF emergency department IV diuretic visits (N=7, 41% of total events).
- For the mITT population, 234 (51.3%) subjects had a HF related medication change

from implant to Month 1, 227 (49.8%) subjects had a HF related medication change from Month 1 to Month 3, and 260 (57.0%) had a HF related medication change from Month 3 to Month 6.

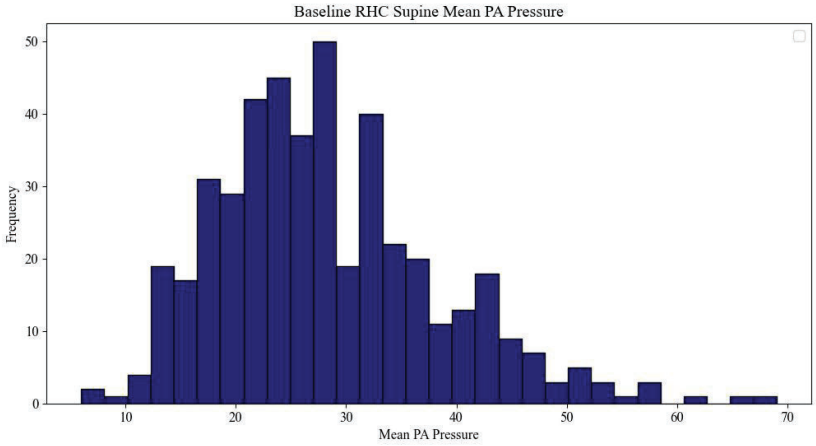
- Overall, the device successfully transmitted PAP data in 67651 out of 68232 days of data collection (>99%).

Change in PAP

Mean pulmonary artery pressure (mPAP) is summarized at all study visits by 'Above Target range', 'Within/Below Target range', and 'Overall' for subjects with a baseline mPAP. Target range is seated trend mPAP 5-20 mmHg.

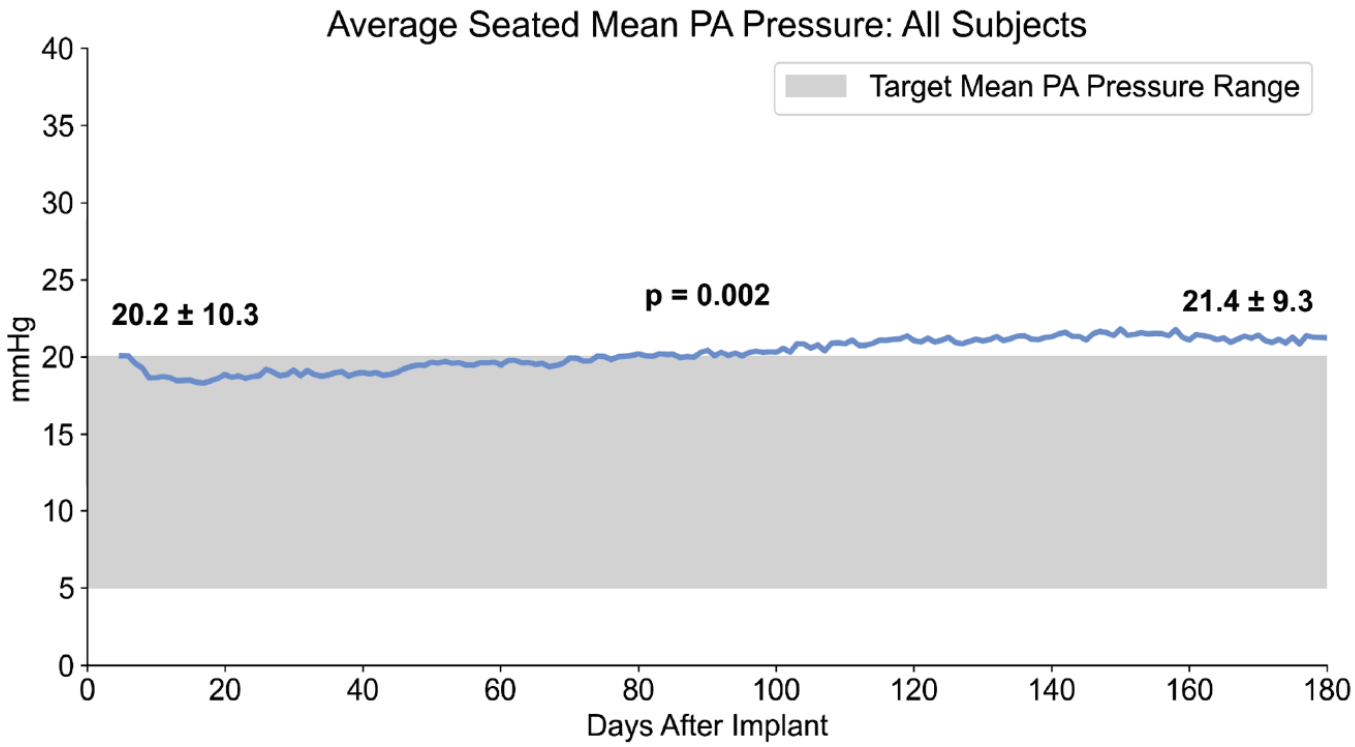
Seated trend mPAP and supine mPAP are external data collected by Endotronix, as measured by the Cordella system, and transmitted by the patients from home. Baseline is defined as the first trend seated mPAP transmitted from the patient within 14 days of the Implant Visit, V3 – Month 1 is defined as the last seated trend within 7 days prior to the visit, V4 – Month 3 is defined as the last seated trend within 7 days prior to the visit, and V5 – Month 6 is defined as the last seated trend within 14 days prior to and 14 day after the visit. Figure 14 shows the baseline distribution of RHC Supine Mean PA Pressure.

Figure 14: Histogram of Baseline Right Heart Catheterization Supine Mean Pulmonary Artery Pressure



In the overall mITT population, the seated trend mPAP increased significantly over 6 months (20.2 ± 10.3 vs. 21.4 ± 9.3 mmHg, p=0.002) as shown in Figure 15.

Figure 15: Average Trend Seated Mean Pulmonary Artery Pressure in the mITT Population



In the Above Target population, the seated trend mPAP decreased significantly over 6 months (29.2 ± 7.7 vs. 26.8 ± 9.2 mmHg, p=0.0006). In the Below/Within Target population, the seated trend mPAP increased significantly over 6 months (12.8 ± 4.9 vs. 17.0 ± 6.8 mmHg, p<0.0001). Summary statistics for the mITT population are shown in **Table 14.**

Table 14: Change in Seated Trend mPAP from Baseline through 6 months for mITT Population

Category	Time	Result	mITT (N=456)	Above Target* (N = 206)	Below/Within Target* (N = 247)
Seated Trend mPAP (mmHg)	Baseline	n	437	197	240
		Missing, n (%)	19 (4%)	9 (4%)	7 (3%)
		mean (SD)	20.2 (10.3)	29.2 (7.7)	12.8 (4.9)
		median	19.12	27.43	13.7
	V3 - Month 1	n	432	199	233
		Missing, n (%)	24 (5%)	7 (3%)	14 (6%)
		mean (SD)	18.9 (11.5)	26.0 (8.8)	12.9 (10.0)
		median	17.62	25.22	12.5
	V4 - Month 3	n	426	194	232
		Missing, n (%)	30 (7%)	12 (6%)	15 (6%)

Category	Time	Result	mITT (N=456)	Above Target* (N = 206)	Below/Within Target* (N = 247)
		mean (SD)	20.3 (9.6)	26.4 (9.2)	15.2 (6.6)
		median	18.83	25.84	15.07
	V5 - Month 6	n	388	171	210
		Missing, n (%)	68 (15%)	35 (17%)	37 (15%)
		mean (SD)	21.4 (9.3)	26.8 (9.2)	17.0 (6.8)
		median	20.4	16.2	17.3
Mean Implant Visit vs. Mean V5 - Month 6		p-value	0.0016†	0.0006†	<0.0001†

mPAP = mean pulmonary artery pressure; * Target = seated trend mPAP 5-20mmHg as first transmitted from home. Baseline cut-off is 14 days from implant; † paired t-test

Change in Medication

Pulmonary artery pressure before and after changes in medication are also provided for the mITT cohort in Table 15. For the mITT cohort, an average increase in pulmonary artery pressures over 2-3 weeks preceded a medication increase. Following the medication increase, there was an average decrease in pulmonary artery pressures over 1-3 weeks for most medication classes.

Table 15: Mean and Standard Deviation of Trend Mean Seated Pulmonary Artery Pressures by Day of Dosage Increases of Various Medication Classes in the mITT Population (N=456)

Med Class	Number Patients	Number Increases	21 Days Before	14 Days Before	7 Days Before	Day Before	3 Days After	7 Days After	14 days After	21 Days After
Diuretic	276	1119	23.0 (8.6)	23.4 (8.5)	23.8 (8.7)	24.3 (8.7)	24.5 (8.6)	23.9 (8.6)	23.7 (8.6)	23.6 (8.4)
RASI	90	134	20.7 (10.5)	20.8 (10.0)	21.1 (10.1)	21.6 (10.0)	21.5 (9.9)	21.1 (9.5)	20.7 (9.0)	21.0 (9.2)
Beta Blocker	88	123	17.9 (9.0)	18.6 (8.7)	18.7 (9.1)	19.4 (8.8)	19.3 (8.6)	19.7 (9.1)	19.8 (9.2)	19.9 (8.8)
SGLT2-I	45	55	22.5 (8.7)	22.7 (9.0)	22.6 (9.1)	22.9 (8.2)	22.9 (7.8)	22.7 (8.1)	22.4 (8.5)	22.2 (8.6)
MRA	90	118	21.5 (8.6)	21.0 (8.5)	22.1 (10.0)	22.3 (9.5)	22.2 (9.1)	22.0 (9.4)	21.8 (9.2)	21.2 (8.6)
Nitrate	25	38	20.4 (11.2)	20.1 (10.7)	21.1 (10.3)	20.9 (9.6)	20.7 (9.5)	20.5 (9.7)	20.7 (9.8)	19.3 (9.6)
HHC	21	36	19.7 (9.2)	20.8 (8.7)	21.5 (10.2)	22.0 (10.2)	22.0 (9.5)	21.4 (10.2)	21.8 (11.1)	22.0 (12.4)

RASI = renin-angiotensin system inhibitor; SGLT2-I = sodium-glucose cotransporter 2 inhibitor; MRA = Minerlocorticoid receptor antagonist; HHC = hydralazine hydrochloride

Subject outcome measures, measured by Kansas City Cardiomyopathy Questionnaire (KCCQ)

In the mITT population, the KCCQ Overall Summary Score (OSS) improved over 6 months (52.8 ± 22.8 vs. 57.8 ± 24.2 points). Descriptive statistics for the KCCQ-OSS for the mITT population are shown in **Table 16**.

Table 16: Kansas City Cardiomyopathy Questionnaire OSS Score for the mITT Population

KCCQ Score	Time	Result	mITT (N=456)
Overall Summary Score	Screening	n	421
		missing (%)	35 (8.0%)
		mean (SD)	52.8 (22.8)
		median	52.6
		min	0.0
		max	100.0
	V3 - Month 1	n	407
		missing (%)	49 (11.0%)
		mean (SD)	55.8 (23.3)
		median	55.73
		min	2.6
		max	100.0
	V4 - Month 3	n	392
		missing (%)	64 (14.0%)
		mean (SD)	56.1 (24.6)
		median	56.68
		min	0.0
		max	100.0
	V5 - Month 6	n	379
		missing (%)	77 (17.0%)

KCCQ Score	Time	Result	mITT (N=456)
		mean (SD)	57.8 (24.2)
		median	58.33
		min	0.0
		max	100.0
Screening vs. V5 - Month 6		p-value	<0.0001†
†Paired t-test			

Functional status improvement, as measured by six-minute walk test (6MWT)

In the mITT population, 6MWT distance increased significantly through 6 months (259.5 ± 121.1 vs. 283.2 ± 123.9 meters, p=0.001). Summary statistics for the mITT populations are shown in **Table 17**.

Table 17: 6-Minute Walk Test through 6 Months for the mITT Population

Category	Time	Result	mITT (N=456)
6MWT Total Distance Walked	Screening	n	436
		missing, (%)	20 (4.0%)
		mean (SD)	259.5 (121.1)
		median	267.74
		min	0.0
		max	780.0
	V5 - Month 6	n	347
		missing, (%)	109 (24.0%)
		mean (SD)	283.2 (123.9)
		median	290.0
		min	0.0
		max	640.0

Category	Time	Result	mITT (N=456)
Screening vs. V5 - Month 6		p-value	0.001†
†Paired t-test			

3. Subgroup Analyses

Main Analysis: Subgroups

Further analyses were undertaken to provide additional information of interest. The study was not specifically powered for the subgroups of the listed baseline characteristics. All p-values are for descriptive purposes only. The p-values are considered nominal.

The following baseline characteristics were evaluated for potential association with safety and effectiveness outcomes:

i. male vs. female
ii. HFpEF vs. HFrEF vs. HFmrEF
iii. White vs. Non-White race
iv. Hispanic vs. Non-Hispanic ethnicity
v. above median BMI vs. below median BMI
vi. NT-proBNP > 1500 pg/mL vs NT-proBNP ≤ 1500 pg/mL
vii. above median eGFR vs. below median eGFR
viii. ischemic vs. non-ischemic HF
ix. cardiac resynchronization therapy vs. no cardiac resynchronization therapy
x. enrollment type: all HFH vs. enrollment type: HFH criteria only vs. enrollment type: NT-proBNP criteria only vs. enrollment type: HFH & NT-proBNP criteria
xi. pulmonary hypertension vs. no pulmonary hypertension
xii. above target range vs. within/below target range
xiii. on SGLT2i at any time in 6-month follow-up vs. not on SGLT2i at any time in 6-month follow-up
xiv. on ARNI at any time in 6-month follow-up vs. not on ARNI at any time in 6-month follow-up
xv. on MRA at any time in 6-month follow-up vs. not on MRA at any time in 6-month follow-up.

The 6-month incidence of HF related hospitalizations or all-cause mortality in all subgroups analyzed was significantly lower than the performance goal (0.43). The only subgroup comparisons that had significantly different event rates were those associated with pulmonary hypertension: pulmonary hypertension vs. no pulmonary hypertension (0.2349 vs. 0.0529, p<0.0001) and Above Target range vs. Below/Within Target Range (0.2540 vs. 0.0734, p=0.0001) and associated with high NT-proBNP: NT-proBNP > 1500 vs. NT-proBNP ≤ 1500 (0.2503 vs. 0.1053, p=0.0026). Results for each subgroup and subgroup comparison are shown in **Table 18**.

Table 18: Primary Efficacy Analysis: Subgroups

Subgroup	Event rate*	95% CI*
White (N=347)	0.1555	0.1114-0.2171
Non-White (N=109)	0.1704	0.1012-0.2866
Hispanic (N=20)	0.1036	0.0259-0.4142
Non-Hispanic (N=436)	0.1608	0.1208-0.2141
Below Median BMI (N=228)	0.1739	0.1159-0.2610
Above Median BMI (N=228)	0.1456	0.0985-0.2151
NT-proBNP > 1500 (N=148)	0.2503	0.1651-0.3796
NT-proBNP <= 1500 (N=298)	0.1053	0.0723-0.1532
Above Median eGFR (N=223)	0.1375	0.0897-0.2109
Below Median eGFR (N=231)	0.1795	0.1247-0.2630
Ischemic HF (N=143)	0.1857	0.1035-0.3333
Non-Ischemic HF (N=313)	0.1453	0.1085-0.1946
Cardiac Resynchronization Therapy (N=82)	0.1276	0.0593-0.2746
No Cardiac Resynchronization Therapy (N=374)	0.1658	0.1259-0.2242
Enrollment Type: All HFH (N=366)	0.1722	0.1271-0.2335
Enrollment Type: HFH criteria only (N=150)	0.103	0.0552-0.1920
Enrollment Type: NT-proBNP criteria only (N=89)	0.1047	0.0509-0.2151
Enrollment Type: HFH & NT-proBNP criteria (N=216)	0.2204	0.1562-0.3109
PH (baseline RHC mPAP > 20 mmHg) (N=264)	0.2349	0.1731-0.3188
No PH (baseline RHC mPAP ≤ 20 mmHg) (N=190)	0.0529	0.0284-0.0983
Above Target (seated mPAP > 20 mmHg) (N=206)†	0.254	0.1815-0.3555
Within Target (seated mPAP 5-20 mmHg) (N=247)†	0.0734	0.0462-0.1166
On SGLT2i at any time in 6-month follow-up (N=297)	0.1591	0.1149-0.2204
Not on SGLT2i at any time in 6-month follow-up (N=159)	0.1585	0.0919-0.2734
On ARNI at any time in 6-month follow-up (N=212)	0.16	0.1061-0.2415
Not on ARNI at any time in 6-month follow-up (N=224)	0.1579	0.1074-0.2322
On MRA at any time in 6-month follow-up (N=336)	0.1631	0.1187-0.2243

Not on MRA at any time in 6-month follow-up (N=120)	0.1475	0.0808-0.2691
*Event rates with 95% confidence intervals were calculated using a negative binomial model		
† From baseline defined as the first trend seated mPAP transmission		
SGLT2i = Sodium-Glucose Transport Protein 2 Inhibitors; ARNI = Angiotensin Receptor/Neprilysin Inhibitor; MRA = Mineralocorticoid Receptor Antagonist; BMI = Body Mass Index; HFH = Heart Failure Hospitalization; NT-proBNP = N-terminal Prohormone of Brain Natriuretic Peptide; HF = Heart Failure; PH = Pulmonary Hypertension; RHC = Right Heart Catheterization; mPAP = Mean Pulmonary Artery Pressure		

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

XI. 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 75 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The low rates of the 6-month incidence of HF hospitalizations or all-cause mortality seen in the PROACTIVE-HF trial are consistent with what has been previously reported for the Cordella PA Sensor System. In the SIRONA 2 trial in Europe, the 6-month incidence of HF related hospitalization or all-cause mortality was 0.20 events per patient 6-month and the 12-month incidence was 0.33 events per patient 12-month.[1,2] Once PROACTIVE-HF was changed to a single arm trial, subjects and their clinicians in the former control arm (Cohort #1) were unblinded to PAP. In the 6 months following unblinding, the rate HF hospitalization or all-cause mortality was 0.13 events per patient 6-month[11] and at 12 months post-unblinding, the rate was 0.34 events per patient 12-month.[12] While the event rate of 0.1589 events per patient 6-month in the PROACTIVE-HF trial is low, these results are congruent with 6-month event rates seen in other published results of the Cordella PA Sensor System, in both Europe and the Unites States.

XIII. 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 Hemodynamics and Heart Failure Diagnostic Device, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The benefits of the device are based on data collected in a single arm clinical study conducted to support PMA approval as described above.

The primary efficacy endpoint of the 6-month incidence of HF related hospitalizations or all-cause mortality in the modified Intent-to-Treat (mITT) population was met. For study success, the upper confidence bound of the observed event rate in the mITT population was required to be less than the performance goal (PG) which was 0.43 events per patient 6-month, or equivalently, that the corresponding p-value from the hypothesis test (6-month primary event rate < PG) was less than 0.025. Furthermore, the observed rate must be less than 0.37. Given that the upper confidence bound of the observed event rate was less than PG (0.2106 vs 0.43), the observed rate was significantly lower than PG (0.1589 vs 0.43; $p<0.0001$), and the observed rate was less than 0.37, all criteria for the primary efficacy were satisfied. The primary efficacy endpoint was tested in a number of subpopulations as prespecified by the PROACTIVE-HF protocol. These analyses were separate from the primary efficacy outcomes and were not endpoint contributing and so the findings here are hypothesis generating. All subgroups of the mITT population analyzed (Male, Female, HFpEF, HFrEF, HFmrEF) met the criteria for primary endpoint success with low rates of HF hospitalizations and mortality across all subgroups.

However, the population initially enrolled into PROACTIVE-HF as the control group in the randomized arm (Cohort #1) did not meet the criteria for efficacy endpoint success although the 6-month incidence of HFH or all-cause mortality was low (0.31 [95% CI: 0.13, 0.72]). Furthermore, the 6-month incidence of HF related hospitalizations or all-cause mortality was higher in Cohort #1 compared to the mITT population (Cohort #2 and Cohort #3) (0.3106 vs. 0.1589, p=0.0859; alpha=0.15) but lower than historical control groups. There was no difference between Cohort #1 and Cohort #2 (0.3106 vs. 0.1557, p=0.2378) event rates. There was an absence of difference between Cohort #2 and Cohort #3 (0.1557 vs. 0.1595, p=0.8979). Recall, the study was not prospectively powered for these analyses, p-values are nominal, and the results are hypothesis generating. However, the differences between Cohort #1 and both Cohort #2 and Cohort #3 may be attributed to the fact that the Cohort #1 population did not have access to PAP (neither did their clinicians) for a median of 170 days in the 6 month follow-up but had access to vital signs for the entire duration of follow-up. Once PROACTIVE-HF was changed to a single arm trial, subjects and their clinicians in Cohort #1 were unblinded to PAP. In the 6 months following unblinding, the rate of HF hospitalization or all-cause

mortality was 0.13 events per patient 6-month and at 12 months post-unblinding, the rate was 0.34 events per patient 12-month.

The primary 6-month incidence of HF related hospitalizations requiring one calendar day change or all-cause mortality was primarily made up of HF related hospitalizations, which occurred with an incidence of 0.1334 [95% CI: 0.0989, 0.1798] events per patient 6-months. The incidence of all-cause mortality was 0.0221 [95% CI: 0.0119, 0.0411] events per patient 6-month. These incidence rates were composed of 60 HF related hospitalizations and 10 all-cause deaths. These results compare favorably with the first randomized trial in PAP-guided HF management (CHAMPION),[7] which reported 6-month incidences of HF related hospitalizations or all-cause mortality of 0.37. More contemporary trials only report 12-month incidences but estimating the 6-month rates via an exponential distribution result in 6-month incidences of HF related hospitalizations or all-cause mortality of 0.31 in GUIDE-HF NYHA III and 0.31 in MONITOR-HF.[3,13] While PROACTIVE-HF did not include emergency department / hospital outpatient IV diuretic visits in the primary efficacy endpoint, these data are reported in the secondary outcomes. Including emergency department / hospital outpatient IV diuretic visits along with HF related hospitalizations and all-cause mortality results in an event rate of 0.1925 [95% CI: 0.156, 0.2375]. Of the 10 all-cause deaths, six were cardiac related resulting in a 6-month incidence of cardiac mortality of 0.0133 [95% CI: 0.006, 0.0295].

In the mITT population, the average seated trend mPAP increased over 6 months (20.2 ± 10.3 vs. 21.4 ± 9.3 mmHg, paired t-test p=0.0016). However, the target range for seated mPAP was 5-20 mmHg and, for those subjects who were above target range at baseline (i.e. congested), there was a significant decrease in seated mPAP over 6 months (29.2 ± 7.7 vs. 26.8 ± 9.2 mmHg, paired t-test p=0.0006). For those subjects below / within target range at baseline (≤20 mmHg), there was significant increase in seated mPAP over 6 months (12.8 ± 4.9 vs. 17.0 ± 6.8 mmHg, paired t-test p<0.0001). It should be noted that, on average, these patients were still in target range at 6 months. The Cordella system is the first PAP-guided HF management system to incorporate seated PAP readings for HF management. As subjects spend most of their waking hours in an upright position, seated measurements may be more relevant for monitoring in ambulatory HF subjects. When subjects move from the supine to seated position, volume shifts may occur leading to venous pooling and seated PAP may be more representative of a subject's volume status under gravitational loading. The Cordella system is also the first PAP-guided HF management system to incorporate daily vital signs with seated PAP readings for HF management. For systolic blood pressure, both in-office (121.8 ± 19.1 vs. 115.9 ± 18.9, paired t-test p-value<0.0001) and home (118.4 ± 20.0 vs. 115.6 vs. 18.1 mmHg, paired t-test p-value 0.0056) readings were significantly lower at 6 months.

In the mITT population, the KCCQ Overall Summary Score significantly improved over 6 months (52.8 ± 22.8 vs. 57.8 ± 24.2 points). Importantly, a change in 5 points is considered to be a small but clinically important change.[15] Functional capacity, as measured by 6MWT improved in the mITT population (259.5 ± 121.1 vs. 283.2 ± 123.9 m).While NT-proBNP did not decrease significantly (p=0.06), the trend was favorable.

Much of the success of PAP-guided HF management relies on subjects sending in their

data and clinicians responding in a timely and appropriate manner to those data. In PROACTIVE-HF, patient compliance was defined as transmitting at least 5 days of Cordella clinical data per week (did not need to be consecutive days). Subject compliance was very good with an average of 88% compliance over 6 months. Put another way, subjects submitted, on average, 6.2 days every week through 6 months. For the sites, compliance was defined as A) acknowledgements of all subjects' vital signs at least two times a week with a maximum of 4 days between data reviews and B) documentation of patient treatment decisions within the PMP system for each notification generated by the system. Here again, compliance was very good with an average of 93% acknowledging of subjects' PAP and vital signs within 4 days of transmission with an average of 2.2 days between transmission and acknowledgment. Furthermore, 93% of the notifications generated by the Cordella system had the related patient treatment decision entered into the system.

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 study's first primary safety endpoint was the freedom from a Device/System-Related Complication (DSRC) through 6 months. Four adjudicated DSRC events were observed in the ITT population during the follow-up and the probability of being free from a DSRC at 6 months post-implant procedure was 99.2%.

None of the DSRCs resulted in permanent subject impairment or death and all subjects recovered without sequelae. The outcomes for DSRCs support an acceptable safety profile for Cordella PA Sensor implantation procedures and follow up, suggesting that even when DSRCs occurs, they can be managed effectively without long-term negative impacts on the patient. The first primary safety endpoint was met. However, with an event rate of 3.0% for all-cause hemoptysis, the event rate of this safety endpoint in the early experience with this new device is numerically higher than prior studies completed to date with similar PAP-measuring devices, such as in CHAMPION (0.2%), GUIDE-HF (0.3%) and MONITOR-HF (2.3%). The study's second primary safety endpoint was the freedom from Pressure Sensor Failure through 6 months. One event of Pressure Sensor Failure was reported and adjudicated and the probability of being free from a Pressure Sensor Failure event at 6 months post-implant procedure was 99.8%. Again, this is similar to what has been reported for the currently approved device. The second primary safety endpoint was met. Throughout the study thus far, there are no other reports on implanted PA sensors failing to provide readings indicating very good sensor stability and system performance.

There were comparable incidences of HF adverse events in the different subject populations, including hospitalizations, emergency department visits, and outpatient office or practice visits. Similar incidences of acute kidney injury and renal dysfunction were observed, along with vascular access site complications and vessel trauma. Peri-procedural hemoptysis was noted in 15 cases and all subjects with hemoptysis recovered.

In ITT and Cohort #1 populations, CEC adjudicated prespecified related Non-DSRC AEs/SAEs summed to seventy total events with (possible) relationship to procedure and/or study device. Ten of the (possibly) procedure related events were also related to

study device and two events were related to study device only.

Fifty-four (54) of related events occurred in ITT population, thirty-eight (38) in prespecified SAE categories and sixteen (16) in category “Other”. The most common were Hemoptysis (n=15, 3.0%; number of events =15) and Vascular Access Site Complications (n =12, 2.4%; number of events =13). Further related events were Conduction Disturbances and Arrhythmias (n =4, 0.8%; number of events =4), Bleeding (n =3, 0.6%; number of events =3), Heart Failure (n =2, 0.4%; number of events =2) and Pulmonary Embolism (n =1,0.2%; number of events =1). In Cohort #1, a total of nine (serious) adverse events related to the procedure and/or study device were adjudicated. These included two instances of bleeding, two events of conduction disturbances and arrhythmias, one of each of vascular access site complication, and vessel trauma. Three procedure related category “Other” events were adjudicated. None of the AEs or SAEs related to the procedure or study device resulted in permanent impairment or death of any subject. With the exception of two instances, all subjects recovered without any lasting effects. One event of "Recovery with Sequelae" pertains to a device explant followed by the subject's full recovery. The second event of "Recovery with Sequelae" was succeeded by an event from which the subject has fully recovered. All subjects who experienced related events have not experienced any further events associated with the Cordella PA Sensor System during the study follow-up.

Observed hemoptysis events were mild or moderate, with most requiring no treatment beyond observation or medication. Interventions were limited to imaging during the RHC, chest X-ray, or CT Angiography. In two cases, intubation was necessary for airway protection, but both instances resulted in patient extubation and patient discharge. However, the occurrence of all-cause hemoptysis was numerically higher (3.0%) than prior studies completed to date with similar PAP-measuring devices, such as in CHAMPION (0.2%), GUIDE-HF (0.3%) and MONITOR-HF (2.3%). Based on internal clinical evaluation and event adjudication during the trial, IFU and physician training documents were updated to address the risks, lowering the Activation Clotting Time (ACT) requirement for the procedure and adding cautionary statements regarding guidewire insertion, all with the objective to decrease the residual risk of hemoptysis.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study(ies) conducted to support PMA approval as described above.

- The 6-month incidence of HF related hospitalizations or all-cause mortality was 0.1589 [95% CI: 0.1200, 0.2106] events per patient 6-month. The observed rate of 0.1589 was significantly less than PG (0.15489 vs 0.43; p<0.0001).
- The primary efficacy endpoint of the treatment group (PAP guided HF management) (0.1589 [95% CI: 0.1200, 0.2106]) was lower than the former control group (Remote Monitoring) (0.3106 [95% CI: 0.1341, 0.7195]) (p=0.0859).
- The KCCQ Overall Summary Score improved over 6 months (52.8 ± 22.8 vs. 57.8 ± 24.2 points).
- Functional capacity, as measured by 6MWT, significantly improved over 6 months (259.5 ± 121.1 vs. 283.2 ± 123.9 m, p=0.001).
- NTproBNP levels trended to improvement at 6 months, but the result was not statistically significant (1731.4 ± 3012.8 vs. 1632.5 ± 2742.4 pg/ml, p=0.0628). The majority of medications used in the treatment of HF decrease NTproBNP significantly. This is a different finding.
- Subjects with baseline mPAP Above Target range on average experienced a mean PAP reduction of 2.4 mmHg at 6 months, from a mean of 29.2 mmHg to a mean of 26.8 mmHg (p=0.0006).
- Subjects experienced a small decrease in weight over 6 months (228.7 ± 56.0 vs. 228.3 ± 54.5 lbs.).

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above.

- Of the 493 subjects in the Intent-to-Treat (ITT) population, four (4) DSRCs were CEC adjudicated as such. The probability of being free from a DSRC at 6 months post implant procedure was 99.2% [95% CI: 97.9%, 99.7%]. The lower bound of the confidence interval, based on the KM method, is higher than the null rate of 90%.
- There were in total 425 site-reported predefined Serious Adverse Events in 196 (39.8%) subjects in the ITT population. There were 27 predefined Serious Adverse Events reported in 22 subjects who entered the cath lab and did not receive an implant. In the implanted subjects, there were 398 predefined Serious Adverse Events reported in 178 subjects.
- Fifty-four (54) non-DSRC AEs or SAEs have been adjudicated by the CEC as (possibly) related to Cordella PA Sensor System or Implant Procedure (38 as per predefined SAE categories/ 16 “Other” events). Ten (10) of the procedure-related events were also adjudicated as (possibly) related to the study device. Two (2) events were adjudicated as related to the study device only.

1. Patient Perspective

   Patient perspectives considered during the review included the evaluation of surveys conducted on Cohort #1 of the study (former control patients).

Subjects signed an informed consent allowing Endotronix to collect this survey data. The subjects previously randomized to the control group were asked to complete an optional subject survey after they were unblinded to Pulmonary Artery Pressure measurements. This survey was completed on the myCordella tablet at 1 month after unblinding and then quarterly until the Year 3 Follow Up Visit.

- No formal patient preference studies were conducted.
- Subject surveys from the SIRONA 2 study indicated 84% of subjects prefer to take PA pressures in the seated position.[2]

In conclusion, given the available information above, the data support that the Cordella Pulmonary Artery Sensor System's probable benefits outweigh the risks.

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. The primary and secondary safety and efficacy endpoints of PROACTIVE-HF were met. The safety profile showed 99.2% freedom from DSRC and 99.8% freedom from pressure sensor failure, with a 3.0% rate of all cause hemoptysis which was numerically higher than prior studies completed to date with similar PAP-measuring devices. In terms of effectiveness, the 6-month incidence of heart failure hospitalization and mortality were low across all populations analyzed. The incidence rate of 0.1589 [95% CI: 0.1200, 0.2106] events per patient 6-month met all criteria for primary endpoint success. While the PROACTIVE-HF aimed to enroll NYHA class III HF patients, the final event rate for the primary effectiveness endpoint (0.1589) was numerically much lower than the average event rate derived from published results from clinically relevant, contemporary studies of NYHA class III HF subjects (as evidenced by an historical performance goal originally set at 0.43). This unexpected finding may warrant further evaluation in future studies. A post-approval study will address any remaining uncertainty in the overall benefit profile of the device.

There was an improvement in quality of life by five points and 6MWT through 6 months. There was high compliance in both subject transmission of daily data and clinician acknowledgement of those transmissions. Of note, these secondary analyses are purely exploratory, not powered and not adjusted for multiple comparisons.

XV. CDRH DECISION

CDRH issued an approval order on 6/20/2024. 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 60 days from the date of this order. Within 30 days of your receipt of this letter, you must submit a PMA supplement that includes a complete protocol of your post-approval study described below. Your 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.

The PAS is a study to collect additional evidence of continued safety and effectiveness in the NYHA Class III patient population as well as to address the uncertainty FDA noted in the enrolled patient population in the PROACTIVE-HF study. The study requirements for this PAS are outlined below:

- Sufficient inclusion criteria to ensure adequate enrollment of NYHA Class III patients including a recent heart failure related hospitalization with a date change
- A minimum of 300 NYHA Class III Heart Failure subjects randomized into treatment and control arms. Control arm may be standard of care or comparable implanted PA pressure monitor.
- A prespecified analysis for a composite primary endpoint demonstrating a positive trend in the reduction of cardiovascular death and heart failure hospitalizations as compared to standard of care or an appropriate comparison of these events versus a comparable implanted PA pressure monitor. Additional relevant analyses to demonstrate benefit to patients should be included such as lowering of PA pressures using the study treatment protocol.
- Enrollment strategy to promote a balance in patients according to sex, race, and ethnicity

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

- First subject enrolled within 6 months
- 20% of subjects enrolled within 12 months
- 50% of subjects enrolled within 18 months
- 100% of subjects enrolled within 24 months

In addition, you 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, you must begin submitting quarterly enrollment status reports every 3 months in addition to your periodic (6-month) PAS Progress Reports, until FDA notifies you otherwise.
- Submit the Final PAS Report three (3) months from study completion (i.e., last subject's last follow-up date).

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).

XVI. 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.

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