RATIONALE AND DESIGN OF THE PROACTIVE-HF TRIAL FOR MANAGING NYHA CLASS III HEART FAILURE PATIENTS WITH THE COMBINED CORDELLA™ PULMONARY ARTERY SENSOR AND THE CORDELLA™ HEART FAILURE SYSTEM

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Highlights

- The PROACTIVE-HF trial is designed to assess the benefit of personalized and proactive management of class III HF patients guided by daily measurements of pulmonary artery pressure (PAP) pressures in combination with weight, blood pressure, heart rate, blood oxygen saturation, and symptoms.

- The investigational Cordella™ Sensor System is designed to achieve high levels of patient engagement and compliance with a small handheld reader placed over an anteriorly implanted sensor facilitating patient-friendly seated PAP measurements and a modern digital health app providing patients with timely education, real-time feedback, and tools for easy two-way communication with the care provider.

- Key trial hypotheses are that HF management using PAP in combination with additional vital sign parameters will provide dual benefits of congestion management and GDMT optimization and that patient engagement and compliance will positively impact remote medical management decisions and patient outcomes.

Title
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Abstract

Background
Optimizing guideline-directed medical therapy (GDMT) and monitoring congestion in heart failure (HF) patients are key to disease management and preventing hospitalizations. A pulmonary artery pressure (PAP)-guided HF management system providing access to body weight, blood pressure, heart rate, blood oxygen saturation, PAP, and symptoms, may provide new insights into the effects of patient engagement and comprehensive care for remote GDMT titration and congestion management.

Methods
The PROACTIVE-HF study was originally approved in 2018 as a prospective, randomized, controlled, single-blind, multi-center trial to evaluate the safety and effectiveness of the Cordella™ PAP Sensor in HF patients with New York Heart Association (NYHA) functional class III symptoms. Since then, robust clinical evidence supporting PAP-guided HF management has emerged, making clinical equipoise and enrolling patients into a standard-of-care control arm challenging. Therefore, PROACTIVE-HF was changed to a single-arm trial in 2021 with pre-specified safety and effectiveness endpoints to provide evidence for a similar risk-benefit profile as the CardioMEMS™ HF System.

Conclusion
The single-arm PROACTIVE-HF trial is expected to further demonstrate the benefits of PAP-guided HF management in NYHA class III patients. The addition of vital signs, patient engagement and self-reported symptoms may provide new insights into remote GDMT titration and congestion management.

**Keywords**
Remote patient monitoring, heart failure, GDMT, clinical trial

**Abbreviations**

- **6MWT** 6-Minute Walk Test
- **ACC** American College of Cardiology
- **ACE** Angiotensin-Converting Enzyme
- **AHA** American Heart Association
- **ARB** Angiotensin Receptor Blocker
- **ARNI** Angiotensin Receptor-Nephrilysin Inhibitor
- **BMI** Body Mass Index
- **BNP** Brain Natriuretic Peptide
- **BP** Blood Pressure
- **dPAP** Diastolic Pulmonary Artery Pressure
- **DSRC** Device System Related Complication
- **ED** Emergency Department
<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
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<tr>
<td>EPPY</td>
<td>Events Per Patient Year</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>GDMT</td>
<td>Guideline Directed Medical Therapy</td>
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<td>HR</td>
<td>Hazard Ratio</td>
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<td>HF</td>
<td>Heart Failure</td>
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<td>HFH</td>
<td>Heart Failure Hospitalizations</td>
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<td>HFSA</td>
<td>Heart Failure Society of America</td>
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<td>HFrEF</td>
<td>Heart Failure with Reduced Ejection Fraction</td>
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<td>Heart Failure with Preserved Ejection Fraction</td>
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<tr>
<td>IDE</td>
<td>Investigational Device Exemption</td>
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<td>KCCQ</td>
<td>Kansas City Cardiomyopathy Questionnaire</td>
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<td>IV</td>
<td>Intravenous</td>
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<td>LVEF</td>
<td>Left Ventricular Ejection Fraction</td>
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<tr>
<td>mPAP</td>
<td>Mean Pulmonary Artery Pressure</td>
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<td>MRA</td>
<td>Mineralocorticoid Receptor Antagonist</td>
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<td>NT-pro-BNP</td>
<td>N-terminal pro B-type Natriuretic Peptide</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
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<td>PA</td>
<td>Pulmonary Artery</td>
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<td>PAP</td>
<td>Pulmonary Artery Pressure</td>
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<td>PG</td>
<td>Performance Goal</td>
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<td>PMP</td>
<td>myCordella™ Patient Management Platform</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SGLT2i</td>
<td>Sodium-Glucose Cotransporter Inhibitor</td>
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<tr>
<td>RCT</td>
<td>Randomized Control Trial</td>
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<tr>
<td>sPAP</td>
<td>Systolic Pulmonary Artery Pressure</td>
</tr>
<tr>
<td>SpO2</td>
<td>Blood Oxygen Saturation</td>
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Background

Approximately 6 million adult Americans live with heart failure (HF) with the projected prevalence expected to increase to 8 million by 2030 as the aging population grows.\textsuperscript{1,2} Despite recent improvements in HF management, HF remains a leading cause of hospital admission in the United States (US), accounting for almost 6.5 million hospital days annually.\textsuperscript{3} The economic burden of HF and related hospitalization is substantial with 1\%-2\% of the total healthcare expenditure in the US allocated to HF, with inpatient admissions accounting for >50\% of this cost.\textsuperscript{4} Once a patient has been diagnosed with HF, establishing appropriate pharmacological therapies and close monitoring of congestion development are key to management of the disease and preventing HF hospitalizations (HFH).\textsuperscript{5}

The most common symptoms upon admission for acute decompensated HF are dyspnea on exertion, orthopnea, fatigue, and peripheral edema. These symptoms reflect an acute or chronic increase in cardiac filling pressures, or congestion.\textsuperscript{6} It has been shown that in HF patients with both reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF), a change in filling pressures can be detected weeks before hospitalization.\textsuperscript{7} Persistent increases in filling pressures typically result in HF decompensation and HFH, whereas when pressures remain stable, the risk of HFH is reduced.\textsuperscript{7}

PAP-guided HF management has been shown to reduce HFH in HF patients with New York Heart Association (NYHA) functional class III symptoms via a targeted treatment strategy of optimizing medical management to actively lower PAP.\textsuperscript{8-11} Device safety and effectiveness for PAP-guided HF management has been established in >25,000 CardioMEMS\textsuperscript{TM} device implants, including >5,000 clinical trial patients from two randomized controlled trials,\textsuperscript{8,11} and >2,000 post-market users with research results published in >150 peer reviewed journals. The
2021 European Society of Cardiology (ESC) HF guidelines recommend (Class IIb) that monitoring of PAP using a wireless hemodynamic monitoring system may be considered in symptomatic patients with HF to improve clinical outcomes.\textsuperscript{12} The 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) guidelines state that the usefulness of wireless monitoring of PAP to reduce the risk of subsequent HF hospitalizations in select patients with NYHA class III symptoms is uncertain (Class IIb recommendation).\textsuperscript{13} This less certain recommendation incorporated the recent GUIDE-HF trial, which showed a significant benefit for PAP-guided treatment across all patient groups when a pre-COVID-19 analysis was performed, but did not reach statistical significance when including post-COVID-19 follow up.\textsuperscript{11}

In the CHAMPION trial, more than twice as many medication changes occurred in the treatment group compared with the control group during the 6-month follow-up, with diuretics being the most frequently adjusted medications in both groups (60.4\% of all HF medication changes). Changes in direct vasodilators and GDMT neurohormonal antagonists also favored the treatment arm, although these medication changes were much less frequent than diuretic changes.\textsuperscript{14} Similarly, in the GUIDE-HF trial, more medication changes were made in the treatment group compared with the control group although it is unclear if this difference is significant and individual medications were not reported. When examining the proportion of patients on GDMT at baseline and then 12 months in the treatment arm, there was no significant difference in GDMT utilization over 1 year.\textsuperscript{11}

The Cordella\textsuperscript{TM} PAP Sensor (Endotronix Inc., Lisle, IL) was designed to enable patient-centric PAP-guided HF management and to assist clinicians in implementing GDMT titration and congestion management in a real-world setting. (Figure 1A-F) Cordella\textsuperscript{TM} provides
comprehensive clinical information remotely, including PAP, body weight, blood pressure (BP), heart rate (HR), blood oxygen saturation (SpO₂), and self-reported symptoms, and has been shown to enable safe and accurate remote monitoring of PAP in the SIRONA 1 (NCT03375710) and SIRONA 2 (NCT04012944) trials.\textsuperscript{15,16} The system is designed to maximize patient engagement with modern digital health tools by providing both vital signs and PAP trends, timely feedback to the patient, and easy communication between patient and provider, all via a single smart tablet. (Figure 1D-F) The PAP reading experience has been enhanced with the design of a small, handheld reader, held over the anterior right chest, which can be used in either seated or supine posture (Figure 1C). The implant procedure is similar to the CardioMEMS procedure\textsuperscript{17} with specific differences to enable anterior PAP readings from a seated posture.\textsuperscript{15}

Besides showing safety and effectiveness, the clinical trials have established the patient-centric experience demonstrating over 94% patient adherence to daily measurement and transmission of vital signs and PAP sensor readings.\textsuperscript{15,16} Furthermore, in the SIRONA 2 trial, patients were instructed to take daily seated and supine PAP readings for the first 3 months and, upon being surveyed on their postural preference, 84% preferred seated compared to supine.\textsuperscript{16}

PROACTIVE-HF study (NCT04089059) was designed to assess whether the favorable clinical results of previous PAP-guided HF management trials are replicable with the Cordella\textsuperscript{TM} PA sensor system across diverse healthcare settings in the US and Europe. PROACTIVE-HF trial is testing the hypothesis that targeted pharmacological intervention to lower and maintain a target range of PAP, combined with a comprehensive patient-centric design, can enable low rates of mortality and HFH in patients with NYHA functional class III symptoms at high risk of congestion based on a history of HFH or elevated N-terminal (NT) pro B-type natriuretic peptide (NT-proBNP).
The current manuscript outlines the original study design and rationale for the PROACTIVE-HF randomized control trial, and, subsequently, the re-design and its associated rationale.

Methods

Original Randomized Control Trial (RCT) rationale

The original FDA-approved investigational device exemption (IDE) study design in 2018 for PROACTIVE-HF was a prospective, randomized, controlled, single-blind, multi-center clinical trial designed to evaluate the safety and effectiveness of the Cordella™ PA Sensor in NYHA functional class III HF patients. The Institutional Review Board of each participating center approved the study protocol, each patient provided written informed consent, and events are adjudicated by a Clinical Endpoint Committee. At the time of original study approval, CHAMPION-HF⁸ was the only prospective clinical trial available, necessitating PROACTIVE-HF to include randomized evidence to establish effectiveness in this patient population.

All patients enrolled into PROACTIVE-HF received the Cordella™ PA sensor, implanted in their right PA. (Figure 1A) After the procedure, patients in the original trial were randomized to either treatment or control groups at a ratio of 1:1. Both patient groups were instructed to take their daily PAP measurements along with their weight, BP, HR, SpO₂, and symptoms by using Bluetooth-connected peripherals. (Figure 1B) Readings were automatically uploaded using a patient tablet. Patient information and daily readings were stored and accessed on a dedicated website, the myCordella™ Patient Management Platform (PMP), which is a secure cloud-based platform used by the healthcare providers to review data, manage patients, and capture clinical decisions. All readings (weight, BP, HR, SpO₂, symptoms, and PAP) were visible and accessible to the healthcare providers of the treatment arm cohort, while only the vital signs were accessible.
to treatment patients. In the control arm, vital signs only (weight, BP, HR, SpO₂, and symptoms) were visible and accessible to the patients and healthcare providers. After 12 months, providers in the control arm were unblinded to PAP data and patients in both arms were able to visualize their own PAP measurements. In this initial design, the primary endpoint was all cause mortality, HFH, and the need for unscheduled Emergency Department (ED) / outpatient intravenous (IV) diuretic treatment at 12 months. The original PROACTIVE-HF trial assumed a 12-month mortality rate in the control group of 0.15 events per patient year (EPPY) with an HFH rate of 0.60 EPPY with the expectation that treatment might lower the 12-month mortality rate to 0.14 EPPY and HFH to 0.45 EPPY. The sample size calculation for the study required 900 patients, with a threshold of 970 enrolled subjects to account for possible early discontinuations. Calculation was based on 80% power and a one-sided alpha of 0.025. The first subject was implanted in February 2020. As outlined below, blinding of patients and practitioners was removed from protocol in December 2021 and the above sample size calculations were revised to meet the new trial design.

Major Inclusion/Exclusion Criteria

Major inclusion/exclusion criteria are listed in Table 1; they are similar to those previously reported for SIRONA 2 and GUIDE-HF. In brief, adults with a diagnosis of HFrEF or HFpEF and NYHA functional class III symptoms are eligible for enrollment in PROACTIVE-HF if they are treated with optimal doses of GDMT for a minimum of 3 months (stable doses at least 30 days prior to enrollment) and the patient had either one HFH within the last year or a persistently elevated NT-proBNP level at the time of screening. The PROACTIVE-HF trial is designed to ensure the inclusion of moderately congested HF patients with higher risk of congestion related events, who have an NT-proBNP > 1500 pg/mL (for an LVEF < 50%) and
> 800 pg/mL (for an LVEF \( \geq 50\% \)). The congestion cut-off for NT-proBNP is higher than that of the GUIDE-HF trial\(^{11}\), which used NT-proBNP levels > 1000 pg/mL (for an LVEF \( \leq 50\% \)) and > 700 pg/mL (for an LVEF \( \geq 50\% \)). A correction for BMI is applied as a 4% reduction per BMI unit that exceeds 25 kg/m\(^2\). The study eligibility committee reviews and approves all potential patients prior to enrollment and implant.

Following implant, patients are asked to measure their PAP daily (typically at the same time each morning) along with their weight, BP, HR, SpO\(_2\), and symptoms for secure wireless transmission. Clinicians are instructed to access the PMP at least once every 4 days and to treat patients per the trial specific treatment guidelines. Patients are contacted weekly during the first month and then monthly thereafter, and as needed for medication changes. Follow-up visits are performed in person at 1, 6, 12, 18, 24 and 36 months, with a virtual visit at 3 months. At each visit, patients undergo physical examination with assessment of their concurrent medications, blood tests (full blood count, renal/liver function tests, coagulation profile, and NT-proBNP), urinalysis, re-assessment of NYHA functional class, administration of the Kansas City Cardiomyopathy Questionnaire (KCCQ)\(^{18}\), a 6-minute walk test (6MWT)\(^{19}\), and determination of adverse events. Echocardiography is performed at screening, 12 months, and 36 months.

A central element of the trial are the treatment guidelines, or the management strategy to optimize and maintain GDMT, with intervention designed to lower PAP to a target range representative of a state of euvolemia. The aim of treatment is optimization of medical therapies [angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB) or angiotensin receptor-neprilysin inhibitors (ARNI), beta blockers, mineralocorticoid receptor antagonists (MRA), diuretics, and sodium/glucose cotransporter-2 inhibitors (SGLT2i)] as appropriate for HF as classified by LVEF, which are then to be titrated against specific mPAP
targets or mPAP trends (Figure 2). For the purposes of patient management, changes in seated mPAP trends, defined as a 7-day average of daily means, are monitored with a target seated mPAP goal between 5-20 mmHg. In order for the 7-day average to be calculated, there must be no more than 2 consecutive missed readings or 3 or less total missing readings in any 7-day moving window. Clinicians may observe and treat based on systolic PAP (sPAP), mPAP, and/or diastolic PAP (dPAP), or even PAP measurements in the supine posture, but the standardized treatment guideline notifications via the PMP are based upon the 7-day average of seated mPAP only. As mentioned, clinicians are required to acknowledge data at least once every 4 days. It is expected that this approach, a moving average filter and the timeliness of data review, will address diurnal PAP variability and be responsive to any trend towards rapid increases in mPAP which may be observed in HFpEF cases.

In PROACTIVE-HF, clinicians are encouraged to closely follow GDMT guidelines in order to titrate medical therapies to mPAP threshold whilst considering the vital sign measurements. This protocol differs from the CHAMPION and GUIDE-HF trials, where the use of medications and the doses prescribed to reach target PAP thresholds were based upon PAP alone. The automated web-based PMP data system used in PROACTIVE-HF flags those patients whose PAP falls outside of a predetermined range and where actionable interventions are required. Along with diuretic management, the addition of concurrent vital sign information available to PROACTIVE-HF providers may promote more favorable adjustments in GDMT.

**Subsequent events and rationale for trial design change**

Following the design of the trial, several events occurred necessitating a change in trial design. First, new prospective clinical evidence was published in 2019-2021 which consistently demonstrated a positive clinical benefit in NYHA functional class III patients. Second, PAP-
guided HF management therapy became more widely reimbursed and accessible to patients outside of a clinical trial setting. Lastly, the COVID-19 pandemic altered the clinical trial landscape, changing patient and human behavior broadly, impacting trial timelines and the willingness of patients to subject themselves to risk without the potential for immediate clinical benefit. With the new evidence supporting the benefit of PAP-guided HF management in recently hospitalized NYHA class III patients, there were equipoise challenges with the randomized trial from a clinical perspective, as practitioners wanted unblinded access to PAP measurements. Additionally, with a PAP-guided HF management technology widely and readily available (CardioMEMSTM), study recruitment was hampered by patient apprehension to enroll in a blinded trial.

To this end, in December 2021, following consultation with the Food and Drug Administration (FDA), PROACTIVE-HF was changed to a single-arm trial, with pre-specified safety and effectiveness endpoints to provide objective evidence of a similar risk-benefit profile to the CardioMEMSTM HF System in NYHA class III subjects (Figure 3).

**Former Control Group**

At the time of crossover to a single-arm, patients in the former control group (Cohort A) were unblinded and both patients and clinicians immediately received access to daily PAP. Patient education material and a longitudinal survey to assess patient experience and knowledge of their PAP data were sent out. Patient follow-up will occur through the 3-year study period. These patients will contribute to the safety but not the effectiveness endpoint. Seventy-two patients were enrolled in the former control group prior to crossover.

**Former Treatment Group + Newly Enrolled Treatment Group**
Patients in the former treatment group (Cohort B) will continue follow up per protocol. All newly enrolled patients are treatment patients (Cohort C). Former treatment group patients plus newly enrolled patients (Cohort B + Cohort C) will contribute to the safety and effectiveness endpoints. Seventy-six patients were enrolled in the former treatment group prior to crossover and event rates for this cohort will remain blinded through the primary endpoint of the single arm.

All patients will maintain the same contact schedule as the original PROACTIVE-HF design: contacted weekly during the first month and then monthly thereafter, and as needed for medication changes. Follow-up visits are performed in person at 1, 6, 12, 18, 24 and 36 months, with a virtual visit at 3 months.

**Statistical considerations**

In order to establish effectiveness, 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, CardioMEMS Post approval study, MEMS-HF, GUIDE-HF (NYHA Class III cohort), and LAPTOP-HF (control group only). 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. Thus, for the primary endpoint of HFH and all-cause mortality (HFH/D) at 6 months, the PG is 0.43 events per patient 6-month and the observed value must be lower than 0.37 events per patient 6-month. For the powered secondary endpoint of HFH/D at 12 months, the PG is 0.70 EPPY and the observed value must be lower than 0.59 EPPY.

Primary Endpoint

The assumed PROACTIVE-HF population 6-month event rate of HFH/D is expected to be 0.34. This assumed event rate is lower than all prior active CardioMEMS™ treatment rates except for GUIDE-HF. While the contemporary GUIDE-HF study observed a 6-month event rate of 0.31 in NYHA class III patients, PROACTIVE-HF has higher NT-proBNP thresholds than the GUIDE-HF cohort, and we expect subjects with higher NT-proBNP levels to more closely align with subjects with a recent HFH, who have higher event rates. The null hypothesis will be rejected if the upper confidence bound for the rate is less than the PG of 0.43, or equivalently, that the corresponding p-value from the hypothesis test is less than 0.025. An observed event rate of less than 0.37 events per patient 6-month and rejection of the null hypothesis indicate that the observed rate is statistically less than the PG, indicating clinically acceptable results and study success. The added requirement for the observed event rate to be less than 0.37 provides further assurance that results are comparable to studies of prior CardioMEMS treatment. The study will implant 450 subjects (Cohort B + Cohort C) leading to an expected evaluable cohort of 406 subjects. With a PG of 0.43 events per patient 6-month and a one-sided 0.025 alpha level, the study will have greater than 80% power assuming a population treatment rate of 0.34 events per patient 6-month.
**Secondary Endpoint**

Similarly, the assumed single-arm PROACTIVE-HF population 12-month HFH/D event rate is expected to be 0.55. This assumed event rate is lower than all prior active CardioMEMS™ treatment rates except for GUIDE-HF (where the event rate was 0.52 EPPY). The rationale for this is the same as for the primary endpoint analysis. A value of 0.70 EPPY will be used for the PG. The null hypothesis will be rejected if the upper confidence bound for the rate is less than the PG, or equivalently, that the corresponding p-value from the hypothesis test is less than 0.025. An observed value of less than 0.59 EPPY and rejection of the null will indicate that the observed rate is statistically less than the PG, indicating clinically acceptable results. Analysis will use the same method as the primary endpoint.

**Safety assessments**

There are two primary safety endpoints. First, freedom from device or system related complications (DSRC) at 6 months will be tested against the null rate of 90%. Secondly, freedom from pressure sensor failure at 6 months will be tested against the null rate of 95%. Both primary safety endpoints are assessed as binary (Y/N) through 6 months. In addition to the two primary safety endpoints with hypothesis tests, the following secondary safety endpoints will be summarized: pressure sensor failure rate throughout the study, frequency of serious adverse events (SAEs) throughout the study, and frequency of implant procedure and procedure related adverse events (AEs) and SAEs.

In addition to the above, several secondary endpoints will also be investigated. Notably, HFH rate, all-cause mortality rate, and ED / outpatient IV diuretic visits will be assessed separately and in various combinations at the 6-, 12-, 18-, 24-, and 36-month time points. Additionally, changes in NT-proBNP, days alive out of hospital, all medication changes, change
in PAP from baseline, and change in PAP before and after exercise will be analyzed. Finally, KCCQ, NYHA, 6MWT will be assessed at each time point and an overall health economic analysis will be analyzed.

**Discussion**

Optimization of GDMT involves titration of multiple evidence-based medications at proven target doses and yields a reduction in HFH and mortality when fully implemented. Despite directives regarding GDMT use, the CHAMP-HF Registry, which assessed outpatient management of stable HFrEF patients, confirmed that with the majority of patients, significant gaps in use and dose of GDMT remain. Even in patients whose treatment tolerance is challenging, titration to the target highest possible dose is still critical and not doing so has been associated with poorer outcomes. With that, the aim of the single-arm PROACTIVE-HF trial is to use PAP-guided HF management plus vital sign measurement and self-reported symptoms as a multisystem care delivery model rather than just a reactive PAP remote monitoring measurement tool.

Treatment guidelines that combine GDMT with diuretic management, as enabled by the Cordella™ PA sensor system, provide a more comprehensive approach to patient management. PROACTIVE-HF is similar to prior studies of PAP-guided HF management, where active pharmacological management is suggested to reduce PAP to a euvoletic target range, with some important differences. The treatment guidelines in PROACTIVE-HF are designed around seated mPAP instead of supine PAP, although the Cordella™ system enables either posture. The majority of patients prefer the seated position, which may lead to higher levels of sustained engagement and compliance. In addition to patient preference and engagement, the seated posture represents a different physiologic state, which may be more representative of
daily living. Unlike prior PAP-guided HF management trials where PAP is the sole physiological metric available from the patients’ home, PROACTIVE-HF patients also transmit vital signs (weight, BP, HR, and SpO₂) and symptoms along with daily PAP. Preventing and managing congestion events by targeting treatment to lower PAP is still the aim in PROACTIVE-HF and, therefore, PAP remains the main trigger of action driving proactive therapy delivery. However, with the additional knowledge of vital signs and symptoms, the appropriate treatment may not always be an immediate diuretic change, which was the usual course of therapy decision in prior studies of PAP-guided HF management. Treatment guidelines in PROACTIVE-HF are triggered by PAP levels, yet clinicians are first encouraged to address precipitating factors underlying congestion such as lifestyle issues and non-compliance with medications, in addition to targeted medication adjustments. Additionally, the inclusion of chemistry panels following medication changes as outlined in Figure 2 will also factor into clinical decision making. To better understand how and why clinicians may adjust medications differently with both PAP and vital sign information available, PROACTIVE-HF is capturing documented reasons behind deviations from the recommended treatment guidelines.

Another important component of the Cordella™ system is patient engagement. The system was designed to improve patient engagement with modern digital health tools by providing both vital sign and PAP trends, feedback to the patient, and easy communication between patient and provider all via a single smart tablet. The PAP reading experience has also been enhanced with the design of a small, handheld reader, held at the anterior chest, easing PAP readings. The former control group (Cohort A) will further investigate patient engagement once patients have access to daily PAP and vital sign trend data.
Conclusion

PROACTIVE-HF trial is expected to further demonstrate the benefits of PAP-guided HF management in NYHA Class III patients by providing new insights into the effect of patient engagement and comprehensive care, including vital signs and patient symptoms, on remote medical management decisions and patient outcomes.

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Conflicts of Interest
Omid Forouzan, Nicholas J. Hiivala, Andrea Sauerland, and Katrin Leadley are employees of Endotronix Inc. All other authors report no financial relationships or conflicts of interest regarding the content herein.

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Figures & Tables

Figure 1
**Figure 1A:** Cordella Pulmonary Artery Sensor

**Figure 1B:** Cordella Patient Kit with vital sign peripherals

**Figure 1C:** Depiction of patient using the handheld myCordella Patient Reader to measure seated PAP in the home environment

**Figure 1D:** Patient App Home Screen as seen on the patient smart tablet.

**Figure 1E:** Cordella Pulmonary Artery Pressure system trends of daily measurements as seen by the clinician through the Patient Management Portal (PMP). The red vertical lines represent clinician notes. (Inset): Daily reading of pulmonary artery pressure waveform. Respiratory fluctuations and secondary features such as the dicrotic notch are evident.

**Figure 1F:** Cordella vital sign trends of daily measurements as seen by the clinician through PMP. The red vertical lines represent clinician notes.
<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>1. Subject has given written informed consent</td>
<td>1. Intolerance to all neuro-hormonal antagonists (i.e., ACE-I, ARB, ARNI, and beta-blockers due to hypotension or renal dysfunction</td>
</tr>
<tr>
<td>2. Male or Female, at least 18 years of age</td>
<td>2. ACC/AHA Stage D refractory HF (including having received or currently receiving pharmacologic circulatory support with inotropes)</td>
</tr>
<tr>
<td>3. Diagnosis and treatment of HF (regardless of LVEF) for ≥ 3 months and NYHA Class III HF at the time of Screening</td>
<td>3. Subjects with history of recurrent pulmonary embolism (≥ 2 episodes within 5 years prior to Screening Visit) and/or deep vein thrombosis (&lt; 3 month prior to Screening Visit)</td>
</tr>
<tr>
<td>4. 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 heart failure therapy in the United States, or current European Society of Cardiology (ESC) guidelines for heart failure treatment in Europe, with any intolerance documented.</td>
<td>4. Subjects who have had a major cardiovascular (CV) event (e.g., myocardial infarction, stroke) within 3 months of the Screening Visit</td>
</tr>
<tr>
<td>5. HF related hospitalization, HF treatment in a hospital day-care setting, or urgent outpatient clinic HF visit for IV diuretics within 12 month (last hospitalization should be 30 days before Screening/Enrollment) and/or N-terminal pro B-type Natriuretic Peptide (NT-proBNP) at time of Screening/Enrollment defined as: a. Subjects with LVEF ≤ 50%: NT-proBNP ≥ 1500 pg/mL. b. Subjects with LVEF &gt; 50%: NT-proBNP ≥ 800 pg/mL. Thresholds for NT-proBNP (for both LVEF ≤ 50% and LVEF &gt; 50%) will be corrected for body mass index (BMI) using a 4% reduction per BMI unit over 25 kg/m25.</td>
<td>5. Unrepaired severe valvular disease</td>
</tr>
<tr>
<td>6. Subjects with congenital heart disease or mechanical/tissue right heart valve(s)</td>
<td>6. Subjects with known coagulation disorders</td>
</tr>
<tr>
<td>7. Subjects with known history of life-threatening allergy to contrast dye</td>
<td>8. 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</td>
</tr>
<tr>
<td>9. Known history of life-threatening allergy to contrast dye</td>
<td>10. Subjects whereby RHC is contraindicated</td>
</tr>
</tbody>
</table>
6. Subjects should be on diuretic therapy

7. Subjects who are physically able to hold the myCordella Patient Reader unit (approximate weight 1.3lb) against the ventral thoracic surface for up to 2 minutes per day while in a seated or standing position, as well as dock and undock the myCordella Patient Reader

8. Subjects with sufficient eyesight, hearing, and mental capacity to respond to the myCordella Patient Reader's audio/visual cues and operate the myCordella Patient Reader

9. Subject has sufficient Cellular and/or Wi-Fi Internet coverage at home

10. Subject agrees to return to the Investigator for all scheduled follow-up visits and can return to the hospital for follow-up

11. Subjects with an active infection at the Cordella PA Sensor Implant Visit

12. Subjects with a Glomerular Filtration Rate (GFR) <25 ml/min or who are on chronic renal dialysis

13. Implanted with Cardiac Resynchronization Therapy (CRT)-Pacemaker (CRT-P) or CRT-Defibrillator (CRT-D) for less than 90 days prior to screening visit

14. Received or are likely to receive an advanced therapy (e.g., mechanical circulatory support or lung or heart transplant) in the next 12 months

15. Subjects who are pregnant or breastfeeding

16. 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

17. Severe illness, other than heart disease, which would limit survival to <1 year

18. Subjects whose clinical condition, in the opinion of the Investigator, makes them an unsuitable candidate for the study

19. Subjects enrolled in another investigational trial with an active treatment arm

20. Subject who is in custody by order of an authority or a court of law

Figure 2: PROACTIVE-HF treatment guidelines
Figure 3: Subject Crossover from Randomized, Controlled to Single Arm Design

**Former RCT TRIAL RANDOMIZATION**
- Control Patients (72 patients)
- Treatment Patients (76 patients)

**FDA APPROVAL TO CHANGE TRIAL DESIGN & RANDOMIZATION STOPS**
- Former Control Patients
- Former Treatment Patients
- Newly Enrolled Patients*
  - Cohort A
  - Cohort B
  - Cohort C

**Patient Engagement Study**
- PAP immediately visible to all patients
  - Included in safety endpoint
  - Not included in efficacy endpoint

**Prospective, Multi-center, Open label, Single Arm Study**
- N=450 implanted
  - Prespecified success criteria: Performance goal, HFH/Mortality rate
  - Primary endpoint: 6-month HFH/Mortality
  - Secondary endpoint: 12-month HFH/Mortality

*Under single arm protocol
Author headshot photograph

Liviu Klein