Statistical Analysis Plan

Protocol Title: A **Pro**spective, Multi-Center, Open L**a**bel, Single Arm Clinical **T**r**i**al E**v**aluating the Safety and **E**fficacy of the Cordella™ Pulmonary Artery Sensor System in New York Heart Association (NYHA) Class III **H**eart **F**ailure Patients

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Statistical Analysis Plan

Sponsor Name: Endotronix

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(PROACTIVE- HF Trial)

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Revision History

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1.0	22-Jun-2020	Natalie Steigerwald	Initial Release Version
2.0	29-Dec-2022	Stone Liu	Updated according to protocol V9.0
2.1	17-Aug-2023	Stone Liu	Repeated the primary safety analysis on ITT additionally. The cutoff for 6 month analysis updated to 180 days from 183 days Added an AE summary for 'Other serious adverse events (AE) CEC adjudicated' Added separate analyses of HFH and all-cause mortality from CEC adjudication results The compression population update to Cohort #1, Cohort #2 and #3 from Cohort #1 and Cohort #2 The secondary endpoint #3 update to Comparison of the number of HF Hospitalizations or Emergency Department/ Hospital Outpatient IV diuretic visits of Cohort #1 and Cohort #2 + #3 at 6 and 12 months post implant from Comparison of the number of HF Hospitalizations or Emergency Department/ Hospital Outpatient IV diuretic visits of Cohort #1 and Cohort #2 at 6 and 12 months post implant The secondary endpoint #14 Change from baseline in PAP parameters collected via CorPASS will not performed for Cohort #1 population

I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

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Glossary of Abbreviations

Abbreviation	Description
ACC	American College of Cardiology
ACE-I	Angiotensin Converting Enzyme-Inhibitors
ADE	Adverse Device Effect
AE	Adverse Event
AHA	American Heart Association
ALT	Alanine Aminotransferase
ARB	Angiotensin Receptor Blockers
ARNI	Angiotensin-Neprilysin Inhibitors
ATC	Anatomical Therapeutic Chemical
AST	Aspartate Aminotransferase
BMI	Body Mass index
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CalEQ	Cordella™ Calibration Equipment
CDAP	Cordella Data Analysis Platform
CE	Conformité Européene/European Conformity
CI	Confidence Interval
CDAP	CorPASS Data Analysis Platform
Cordella System	Cordella™ Heart Failure System
cm	Centimeters
CorPASS	Cordella™ Pulmonary Artery Sensor System
CRO	Contract Research Organization
CRP	C- Reactive Protein
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy Defibrillator
CRT-P	Cardiac Resynchronization Therapy Pacemaker P
CS	Clinically Significant
CV	Cardiovascular
eCRF	Electronic Case Report Form

Abbreviation	Description
DD	Device Deficiency
dPAP	Diastolic Pulmonary Artery Pressure
DSMB	Data Safety Monitoring Board
DSRC	Device/System Related Complication
ED	Emergency Department
ECG	Electrocardiogram
GDMT	Guideline Directed Medical Therapy
GFR	Glomerular Filtration Rate
HF	Heart Failure
HFH	Heart Failure Hospitalization
HFEF	Heart Failure Ejection Fraction
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HR	Heart Rate
INR	International Normalized Ratio
ITT	Intent to Treat
IWRS	Interactive Web Response System
KCCQ	Kansas City Cardiomyopathy Questionnaire
lb	Pound
LVEDD	Left Ventricular End Diastolic Dimension
LVEF	Left Ventricular Ejection Fraction
MAR	Missing at Random
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mITT	Modified Intent to Treat
MNAR	Missing not at Random
mPAP	Mean Pulmonary Artery Pressure
N/A	Not Applicable
NCS	Not Clinically Significant
NYHA	New York Heart Association

Abbreviation	Description
PT	Preferred Term
PAP	Pulmonary Artery Pressure
PCWP	Pulmonary Capillary Wedge Pressure
pH	Potential of Hydrogen
PMA	Premarket Approval
PMP	myCordella™ Patient Management Portal
PP	Per protocol
PTT	Partial Thromboplastin Time
QC	Quality Control
QTc	Corrected QT Interval
RAP	Right Atrial Pressure
RBC	Red Blood Cell
RHC	Right Heart Catheterization
RVP	Right Ventricular Pressure
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effects
SAP	Statistical Analysis Plan
SD	Standard Deviation
SI	Standard International System of Units
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SpO2	Peripheral capillary oxygen saturation
sPAP	Systolic Pulmonary Artery Pressure
SOC	System Organ Class
SOP	Standard Operating Procedure
TFL	Table, Figure and Listing
WHO	World Health Organization
UADE	Unanticipated Adverse Device Effect

1. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

1.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, figures, and listings. Health Economic analysis will be covered in a separate SAP.

Assessment of protocol deviations as minor or major for the definition of the analysis sets remains with the Sponsor.

1.2. Timings of Analyses

Main analysis will be performed after all Cohort #2- Previously enrolled Treatment Arm subjects and Cohort #3- Newly enrolled subjects completed the Month 6(V5) study visit or discontinued earlier. This main analysis will include all endpoints and analyses described in the SAP as far as data allow. The cleaning process will be completed at this stage, saying that the main analysis will be based on clean and coded data. Protocol deviations will be assessed and analysis sets will be defined following Syneos Health SOP (Blind) Data Review and Definition of Analysis Sets (3911) prior to the cut-off date for database (soft) lock. At this stage it will be decided if the analysis based on the Per-protocol population will be performed. Analysis will be performed on all analysis sets deemed relevant for the analysis. Listings will include all data collected until the cut-off date, by visit summaries will include data until V5 (Month 6), summaries (e.g. medication, or adverse events) without visit information will include all data until the cut-off date.

Additionally, an analysis on safety data will be performed once, the first 50 subjects which have been implanted with the Cordella PA Sensor have completed V4, Month 3 and also when 100 subjects have completed V3, Month 1. These safety analyses may occur at the same time depending on the timing of study visits. Analysis will be done on as much as possible clean and coded safety data.

The follow-up (final) analysis is planned after all subjects have completed the final study visit (V9, Year 3) or terminated early from the study.

An independent Data Safety Monitoring Board (DSMB) will review descriptive summaries of accumulating safety and subject disposition data on regular basis. Further description of the DSMB analyses can be found in the DSMB Statistical Analysis Plan Version 3.1 dated 07-Feb-2022 [1] and the DSMB charter Version 4.0 dated 04-Mar-2022 [1]. The study team from Syneos Health Biostatistics will perform the analyses.

The cut-off time point for the safety analysis and first two DSMB meetings expected to the identical. Outputs described in the DSMB SAP will cover the safety and DSMB analysis.

2. Study Objectives

2.1. Study Objective

To demonstrate safety and efficacy of the Cordella PA Sensor System.

2.2. Brief Description

This is a prospective, open-label, single arm, multi-center clinical trial evaluating the safety and efficacy of the Cordella™ Pulmonary Artery Sensor System in New York Heart Association (NYHA) Class III heart failure (HF) subjects compared to a Performance Goal (PG).

All eligible subjects get implanted the Cordella PA Sensor. As part of the Cordella PA Sensor System (CorPASS), it intends to measure, record, and transmit pulmonary artery pressure (PAP) data from NYHA Class III heart failure patients at home to clinicians for assessment and patient-centered HF management, with the goal of reducing heart failure hospitalizations.

The study is planned to be conducted in up to 120 sites in the United States and Europe. The study population includes male and female subjects, ≥ 18 years of age with a diagnosis of NYHA Class III heart failure.

With this amendment to the protocol/CIP, subjects will be categorized into three (3) different cohorts:

1. Cohort #1- Previously enrolled Control Arm subjects
    - Subjects in this cohort will be unblinded to their PAP measurements and informed about their previous group assignment and continue their Follow-up visit schedule
    - Additionally, subjects will be asked, throughout the remaining Follow-up period, to complete a regular subject survey on their experience with PAP Measurements and PAP Values.
    - Clinicians will be unblinded to their PAP measurements and start managing the patients to target PA pressures per protocol/ CIP and according to Guideline Directed Medical Therapy (GDMT)
    - Additionally, the clinical site will be asked to contact the subject on a regular basis to discuss their PAP values
    - Separate analysis (safety and effectiveness) will be performed for Cohort #1
2. Cohort #2- Previously enrolled Treatment Arm subjects
    - As of month 12 subjects in this cohort will be able to see their own PAP measurements for the remaining duration of the study.
    - Clinicians will continue to manage the patients to target PA pressures per protocol/CIP and according to GDMT
    - All primary and secondary safety and effectiveness analyses will be performed
3. Cohort #3- Newly enrolled subjects

- Subjects will participate in the Screening/ Enrollment Visit, Cordella PA Sensor Implant Visit, and Follow-Up Visits.
- Clinicians will manage 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 will be performed.

Up to 450 subjects are planned to be enrolled and successfully implanted with the Cordella PA (consisting of subjects from Cohort #2 and Cohort #3 below). These subjects will be the basis for the primary study analysis. Additionally, up to 85 subjects (cross- over from former Control Arm) will continued to be followed in Cohort #1.

To be enrolled into the study, subjects must be receiving stable Guideline Directed Medical Therapy (GDMT) for HF per current American Heart Association (AHA)/American College of Cardiology (ACC) guidelines as standard-of-care for HF therapy in the United States and Europe, with any intolerance documented for at least 30 days. This will be verified by the trial specific PROACTIVE-HF Clinical Eligibility Committee.

Subjects must be diagnosed with heart failure for a minimum of 3 months, are clinically stable, have an increase of NT-proBNP and a 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)

Potential subjects are to be identified by the Investigator and research staff with the study Inclusion and Exclusion criteria in mind. At Screening, subjects are fully informed on what to expect with study participation to maintain a high study participation retention rate. As part of the study Implant Visit, subjects undergo a training on the at-home use of the Cordella™ Heart Failure System (Cordella System) to ensure compliance with the web-based clinical care management component of the Cordella™ Heart Failure System. Throughout the study, subjects will continue to be followed closely to ensure study compliance as well as continued study participation

At the Screening/ Enrollment Visit, subjects review and sign the informed consent form prior to any study-related procedures performed. Based on Screening Visit results, the Investigator confirms and documents study eligibility for each subject. As part of the study screening process, subjects will be scheduled for a RHC and PA Sensor Implant procedure.

At the Implant Visit (V2), the Cordella PA Sensor, which is pre-mounted on a catheter Delivery System, is delivered according to the system's Instructions for Use. Once deployed, the Sensor PAP readings are calibrated using the system's fluid-filled catheter. The calibration coefficients for that Sensor/subject are stored in a database, allowing for consistent PAP calculations throughout the study duration.

Below enrollment stopping rules will be considered during the study.

1) to have sufficient number of women representatives in the study, it is anticipated to include at least 35 % women out of the planned population. Therefore, the inclusion/enrollment of the men subjects will be limited to 65% at the most.
2) to have sufficient number of heart failure with preserved ejection fraction (HFpEF) representatives in the study, it is anticipated to include at least 45 % HFpEF subjects out of the planned population.

Therefore, the inclusion/enrollment of the heart failure with reduced ejection fraction (HFrEF) subjects will be limited to 55% at the most.

Subjects are observed until stable and discharged home with instructions to take their PAP measurements daily (e.g. same time each morning) along with their weight, BP, HR and SpO2, which are wirelessly transmitted to a secure website. Subjects also receive a Cordella™ PA Sensor System implant card, a Patient User's Manual, and a Technical Support number to contact Endotronix representatives with any questions.

The clinician will contact all subjects on a pre-determined call schedule basis to discuss their health status and all patients will be treated according to GDMT.

Visibility to patients' daily data trends will enable the clinician to proactively manage the patients to target PA pressures per protocol and according to GDMT.

Subjects return for follow up visits at 1, 6, 12, 18, 24 months and Year 3 after the Cordella PA Sensor implant, or until study termination. The 3-month follow-up visit will be performed as remote/ virtual Telemonitoring visit.

A subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary reason for termination has to be recorded in the Electronic Case Report Form (eCRF). In addition, efforts have to be made to perform all procedures scheduled for the Month 6 (V5) visit if discontinuation is prior to that visit, or the year 3 (V9) visit if discontinuation is after year 2 but before Year 3. Subjects who are withdrawn may be replaced with new subjects for evaluation upon Sponsor approval.

The primary reason for discontinuation or withdrawal of the subject from the study is collected using the following categories:

- Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful.
- Voluntary withdrawal. The subject wishes to withdraw from the study. The reason for withdrawal, if provided, recorded in the eCRF.
- Principal Investigator withdrawal due to failure to comply with trial requirements or subject is uncooperative or refuses to continue in the trial
- Study termination. The sponsor, Institutional Review Board (IRB), or regulatory agency terminates the study
- Other

After completion of the last study visit (V9) the subject continues to participate in the site-specific Heart Failure Follow-up program.

Main analysis to demonstrate durability of the treatment effect is planned to be performed at the timepoint, when all Cohort #2 and #3 subjects have completed 6 months of follow-up or discontinued study earlier. At this timepoint the complete analysis as defined in the SAP will be performed, including definition of the protocol deviations and analysis sets. The analysis will be done on the clean and coded data.

Once all subjects completed the final study visit (V9) or terminated early from the study, a follow-up analysis will be done. For the follow-up analysis, the complete set of outputs will be refreshed based on the data available at study end.

DSMB meetings are planned for the study and will follow the scheduled defined in the DSMB charter.

2.3. Subject Selection

Subjects in this study are male or female NYHA Class III heart failure patients at least 18 years of age. Subjects must be diagnosed with heart failure for a minimum of 3 months, are clinically stable, have an increase of NT-proBNP and a HF related hospitalization, HF treatment in a hospital day-care setting, or urgent outpatient clinic HF visit for IV diuretics within 12 months (last hospitalization should be 30 days before Screening /Enrollment). Subjects must also meet certain physical requirements necessary for the Cordella PA Sensor implant and functionality of the Cordella System as outlined in the study Inclusion/Exclusion Criteria below.

2.3.1. Inclusion Criteria

In order to be eligible to participate in this study, each subject must meet all of the following criteria:

1. Subject has given written informed consent
2. Male or female, at least 18 years of age
3. Diagnosis and treatment of HF (regardless of left ventricular ejection fraction (LVEF)) for ≥ 3 months and NYHA Class III HF at time of Screening
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 HF therapy in the United States, with any intolerance documented.
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 (NTproBNP) at time of Screening/ Enrollment defined as:
    a. Subjects with LVEF ≤ 50%: NT-proBNP ≥ 1500 pg/mL.
    b. 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
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 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 treating Investigator for all scheduled follow up visits and can return to the hospital for follow up

2.3.2. Exclusion Criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1. Intolerance to all neuro-hormonal antagonists (i.e., intolerance to angiotensin converting enzyme-inhibitors (ACE-I), angiotensin receptor blockers (ARB), angiotensin-neprilysin inhibitors (ARNI), and beta-blockers) due to hypotension or renal dysfunction

2. ACC/AHA Stage D refractory HF (including having received or currently receiving pharmacologic circulatory support with inotropes)
3. 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
4. Subjects who have had a major cardiovascular (CV) event (e.g., myocardial infarction, stroke) within 3 months of the Screening Visit
5. Unrepaired severe valvular disease
6. 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)
7. Subjects with known coagulation disorders
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
9. Known history of life threatening allergy to contrast dye.
10. Subjects whereby RHC is contraindicated
11. Subjects with an active infection at the 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 P (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

2.4. Determination of Sample Size

2.4.1. Primary Efficacy Endpoint (at 6 months post- implant)

To meet the 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. Furthermore, observed event rates in the single arm PROACTIVE-HF should be lower than observed event rates in the control arm of CardioMEMS studies.

Thus, we set the performance goal (PG) as the LOWER of 1) the meta-analysis upper bound confidence interval of CardioMEMS treated patients, and 2) the meta-analysis estimates of CardioMEMS control patients, further adjusted down by potential impact of SGLT2i.

Furthermore, we also require that the single arm PROACTIVE-HF observed event rate is LOWER than both 1) the meta-analysis estimate of CardioMEMS treatment patients, and 2) the lowest observed event rates of CardioMEMS control patients, further adjusted down by potential impact of SGLT2i.

The primary endpoint will be the 6 month incidence of HF related Hospitalizations (HFH) or all-cause mortality compared to PG.

The endpoint PG is based on a random effects meta-analysis for the log-transformed incidence rate fit via restricted maximum likelihood. Results are back transformed to the rate scale. Calculations were performed in R version 3.6.3 with the "metafor" package.

The mean 6 month event rate from the meta-analysis of prior control studies is 0.46, or 0.43 on an adjusted basis to account for SGLT2i inclusion in the guidelines (Adjustment applied assuming 50% use of SGLT2i at the average hazard ratio observed across EMPEROR Preserved, EMPEROR REDUCED, DAPA-HF for NYHA III subjects.). A 6 month event rate of 0.43 also represents a value just below both the highest event rate observed across the CardioMEMS treatment studies (0.44 in MEMS-HF) and the upper bound of the overall meta-analytic treatment estimate (0.44). Taking the totality of results from the meta-analysis of active treatment trials, individual results of active treatment trials, as well as the meta-analysis of control trials, we set the primary endpoint performance goal (PG_6) at 0.43.

Furthermore, the mean 6 month event rate from the meta-analysis of prior treatment studies is 0.38, with both the CHAMPION (0.37) and GUIDE-HF (0.31, NYHA class III) treatment groups with event rates lower than the mean. The lowest 6 month event rate across CardioMEMS control studies of 0.39 occurred in GUIDE-HF (NYHA class III), where modest use of SGLT2i occurred during the trial. We conservatively adjust this lowest observed control event rate down to 0.37 to account for increased SGLT2i utilization.

The table below outlines the data sources used to derive a PG for this endpoint.

Since patient level data was not available and summary data was limited in scope, analysis was based on the numbers of events reported from each study and the number of enrolled subjects was for the denominator, assuming all subjects were followed for the corresponding time period. Accordingly, the estimates are likely conservative underestimates of true rates since complete follow-up on all subjects was unlikely.

For studies reporting only 12-month rates, estimates of 6 month rates were estimated via an exponential distribution. For example, for a study with a reported enrollment n and 12-month rate, r_{12}, we calculated the 6 month rate, r_6, as:

$$r_6 = 1\text{-}\exp(\log_n(1- r_{12})/2)$$

where the division by two (2) accounts for a calculation of the rate for half the follow-up time. When possible, events of each type (HF related hospitalization and death) were calculated separately and summed to produce the composite event counts and the corresponding composite rate. Rates are calculated as numbers of events over numbers of subjects.

Active Treatment - updated 6 Month Rates with calculation details

Study/Publication	Number of Subjects[1]	Events	Rate[2]	Details
CHAMPION [3]	270	99	0.37	- 6-month HFH rate reported as 0.31, yielding approx. 84 events - 15 deaths reported

				- Adding calculated 6-month HFH events and deaths yields 99 events
MEMS PAS [4]	1200	493	0.41	- 6-month rate calculated via reported 12-month rate of 0.54 - Calculated 6-month HFH rate of 0.32, yielding 386 events - 107 deaths reported - Adding calculated 6-month HFH events and deaths yields 493 events
MEMS-HF [5]	234	102	0.44	- 6-month HFH calculated via reported 12-month rate of 0.60 - Calculated 6-month HFH rate of 0.37, yielding 86 events - 16 deaths reported - Adding calculated 6-month HFH and deaths yields 102 events
GUIDE-HF [6] – NYHA class III only	322	100	0.31	- Reported 12 month rate of 0.431/0.089 for HFH/D, for composite of 0.52. - Assuming exponential rate, calculated 6 month rate (events) is 0.31 (100) - Events calculated as 322 subjects x 0.31
Estimate (CI)			0.38 (0.33, 0.44)	

[1] Numbers of subjects are those treated subjects estimated to be followed for 6-month events.

[2] Estimates for events are based on either reported results or are estimated from published figures. For studies reporting 12 month results, 6 month rates were estimated based on exponential rates.

Altogether, for study success, the upper confidence bound of the observed event rate for the planned study must be less than the PG_6 (0.43) and the observed event rate must be less than 0.37. Evaluating the upper bound of the confidence interval for the rate ensures that 1) the observed rate will be comparable to prior studies of active treatment (highest observed value = 0.44), 2) the observed rate will be less than the meta-analytic value derived from prior studies of treatment and control, and 3) the observed rate will be less than the lowest rate observed in the control studies (GUIDE HF). 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 assumed PROACTIVE-HF population event rate 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 an event rate of 0.31 (NYHA Class III), PROACTIVE-HF has higher NTproBNP thresholds than the GUIDE-HF cohort and we expect subjects with higher NTproBNP levels to more closely align with subjects with a recent hospitalization, which have higher event rates. The mathematical statement of the null and alternative hypothesis is as follows:

$H0$: $r_6 \geq PG_6$

H_A: $r_6 < PG_6$

where r_6 is the 6-month rate of primary endpoint events and PG_6 is the performance goal. A value of 0.43 will be used for the goal. The null hypothesis will be rejected if the upper confidence bound for the rate is less than the performance goal, or equivalently, that the corresponding p-value from the hypothesis test is less than 0.025. An observed rate of less than 0.37 and rejection of the null hypothesis indicate that the observed rate is statistically less than the performance goal, indicating clinically acceptable results and

study success. Analysis will be based on a Poisson regression approach for the number of events, with the log follow-up time as an offset term. Sensitivity analyses using a negative binomial approach to capture within-subject correlation will be performed.

The study will implant 450 subjects (combined in Cohort#2 and Cohort#3) leading to an expected evaluable cohort of 406 subjects. With a goal 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. Calculations are based on a one-sample Poisson rate test and were performed with PASS 2021.

2.4.2. Additional 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 mean 12 month event rate from the meta-analysis of prior control studies is 0.75, or 0.70 on an adjusted basis to account for SGLT-2i inclusion in the guidelines (Adjustment applied assuming 50% use of SGLT2i at the average hazard ratio observed across EMPEROR Preserved, EMPEROR REDUCED, DAPA-HF for NYHA III subjects.). A 12 month event rate of 0.70 represents a value just below the highest event rate observed across the CardioMEMS treatment studies (0.73 in MEMS-HF) and the upper bound of the overall meta-analytic treatment estimate (0.74). Taking the totality of results from the meta-analysis of active treatment trials, individual results of active treatment trials, as well as the meta-analysis of control trials, we set the secondary efficacy endpoint of performance goal (PG_{12}) at 0.70.

Furthermore, the mean 12- month event rate from the meta-analysis of prior treatment studies is 0.64, with both the CHAMPION (0.6) and GUIDE-HF (0.52, NYHA class III) treatment groups with event rates lower than the mean. The lowest 12 month event rate across CardioMEMS control studies of 0.63 occurred in GUIDE-HF (NYHA class III only), where modest use of SGLT2i occurred during the trial. We conservatively adjust this lowest observed control event rate down to 0.59 to account for increased SGLT2i utilization.

The table below outlines the data sources used to derive a PG for this endpoint.

Active Treatment - updated 12 Month Rates with calculation details

Study/Publication	Number of Subjects[1]	Events	Rate[2]	Details
CHAMPION [7]	270	162	0.60	- HFH rate of 0.46, yielding approx. 124 events - Mortality rate of 0.14, yielding approx.38 events - Total events = 124 + 38
MEMS PAS [4]	1200	840	0.70	- HFH rate of 0.54, yielding 648 events - Mortality rate of 0.16, yielding 192 events - Total events = 648 + 192
MEMS-HF [5]	234	171	0.73	- HFH rate of 0.60, yielding 140 events - Mortality rate of 0.13, yielding approx. 30 events - Total events = 140 + 31
GUIDE-HF [8] – NYHA class III only	322	167	0.52	- HFH rate of 0.431 + plus death rate of 0.0897 - Composite rate = 0.52 - Total events = 322 subjects x 0.52
Estimate (CI)			0.64 (0.55, 0.74)	

Altogether, for study success, the upper confidence bound of the observed event rate for the planned study must be less than PG_{12} (0.70) and the observed event rate must be less than 0.59. Evaluating the upper

bound of the confidence interval for the rate ensures that 1) the observed rate will be comparable to prior studies of active treatment (highest observed value = 0.74), 2) the observed rate will be less than the meta-analytic value derived from prior studies of treatment and control, and 3) 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 0.59 provides further assurance that results are comparable to studies of prior treatment.

The assumed PROACTIVE-HF population 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. While the contemporary GUIDE-HF study (NYHA class III only) observed an event rate of 0.52, PROACTIVE-HF has higher NTproBNP thresholds than the GUIDE-HF cohort and we expect subjects with higher NTproBNP levels to more closely align with subjects with a recent hospitalization, which have higher event rates. The mathematical statement of the null and alternative hypothesis for the first secondary efficacy is as follows:

$H0$: $r_{12} \geq PG_{12}$

H_A: $r_{12} < PG_{12}$

where r_{12} is the 12 month rate of secondary endpoint events and PG_{12} is the performance goal. A value of 0.70 will be used for the goal. The null hypothesis will be rejected if the upper confidence bound for the rate is less than the performance goal, or equivalently, that the corresponding p-value from the hypothesis test is less than 0.025. An observed value of less than 0.59 and rejection of the null will indicate that the observed rate is statistically less than the performance goal, indicating clinically acceptable results. Analysis will be based on a Poisson regression approach for the number of events, with the log follow-up time as an offset term. Sensitivity analyses using a negative binomial approach to capture within-subject correlation will be performed.

Sample size calculations for the first secondary endpoint were performed in PASS 2021 and based on an assumed population event rate of 0.55, the sample size of 450 subjects would provide approximately 95% power for the secondary endpoint based on a one-sided 0.025 alpha level. If 406 subjects are followed for 12 months, approximately 95% power will be provided, so that the planned sample size is sufficient in light of potential attrition.

Formal hypothesis testing for the purposes of labeling claims for the first secondary efficacy endpoint will only be performed if the null hypothesis for the primary efficacy endpoint is successfully rejected.

This gatekeeping approach preserves the overall type I error rate. Any other calculated p-values and confidence intervals for secondary endpoints will be nominal, without adjustment for multiple comparisons.

2.4.3. Primary Safety Endpoints

There are two primary safety endpoints.

Freedom from device or system related complications at 6 months will be tested against the null rate of 90%. A sample size of 450 patients provides greater than 95% power assuming a population rate of 95% for the freedom-from-event rates for device/system related complication at 6 months. Power would still be maintained at this level for an evaluable sample size of 406.

Similarly, Freedom from Pressure Sensor Failure at 6 months will be tested against the null rate of 95%. A sample size of 450 patients provides approximately greater than 95% power assuming a population rate of approximately 98.4%, for the pressure sensor failure at 6 months endpoint. Power would still be maintained at this level for an evaluable sample size of 406.

Mathematical statements of the null and alternative hypothesis for each test are as follows:

H_0: $S1 \geq PG_{s1}$

H_A: $S1 < PG_{s1}$

And

H_0: $S2 \geq PG_{s2}$

H_A: $S2 < PG_{s2}$

where S1 and S2 represent the freedom-from-event rates for device/system related complication at 6 months, and pressure sensor failure at 6 months respectively, and PGS1 and PGS2 represent the corresponding performance goals with values expressed as a proportion of 0.90 and 0.95 respectively.

Each of these will be assessed within among all patients who underwent a device implant by estimating freedom from the event of interest at 6 months by the Kaplan-Meier method. The proportion event free at 6 months and the corresponding two-sided 95% confidence interval will be compared to the null rate. We use a one-sample test of binomial proportions with a two-sided Type I error rate of 5% to estimate the power available for these analyses.

2.5. Treatment Assignment & Blinding

This is an open-label study.

All subjects get implanted the Cordella PA Sensor in conjunction with a RHC procedure. The implantation takes place at the Implant Visit (V2). After deployment, the Sensor PAP is calibrated using a standard-of-care fluid-filled catheter for independent reference measurements. The calibration coefficients for that Sensor/Reader/Subject are stored in a database, allowing for accurate PAP calculations throughout the study duration.

Also, at the Implant Visit, eligible subjects will be provided with the commercially available Endotronix Cordella System to measure BP, HR, SpO2 and weight.

Subjects are observed until stable and discharged home with instructions their PAP measurements daily (same time each morning) along with their weight, BP, HR and SpO2, which are wirelessly transmitted to a secure website.

2.6. Study Device

The investigational device is Cordella™ PA Sensor System.

The Cordella PA Sensor System comprises 7 subsystems that operate together to take daily PAP readings at a patient's home and transmit the results to a care provider for evaluation

1. Cordella Sensor
2. Cordella Delivery System
3. myCordella Patient Reader
4. Reader Dock
5. Cordella Calibration Equipment (CalEQ)
6. myCordella Tablet*
7. Cordella Data Analysis Platform (CDAP)

For use in the proposed clinical trial, Endotronix intends to use the system in conjunction with Endotronix's commercial Cordella Heart Failure System (Cordella System). The Cordella System collects, records, and transmits physiologic data and communications from the patient at home to clinician(s) for assessment, patient communication, and patient-centered HF management.

It contains the following components:

1. myCordella Patient App
2. myCordella Patient Management Portal (PMP)
3. myCordella Tablet*,**
4. Up to 3 commercially available Medical Devices that patients use at home to collect data: weight, BP, HR and SpO2

* the myCordella Tablet for the Cordella System and CorPASS systems are one and the same.

** not a medical device in accordance with the 21st Century Cures Act.

The subjects are trained at the clinical site by a trained Clinical Site Delegate or Endotronix representatives on the set up and use of the Cordella System during the Screening/Enrollment Visit and for the the Cordella PA Sensor System at the Implant Visit (V2). Visits to the subject's home by an Endotronix Representative may be required throughout the study to provide troubleshooting, servicing, and maintenance of the system.

More detailed information about the study device can be found in Section 2 of the protocol.

2.7. Study Procedures and Time and Event Schedule

For an overview of the timing of the clinical and laboratory measurements see Appendix 1: Time and Event Schedule.

3. Endpoints

3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the 6 month incidence of HF related Hospitalizations (HFH) or all-cause mortalities.

3.2. Primary Safety Endpoints

1. Freedom from device/system related complication at 6 months
2. Freedom from pressure sensor failure at 6 months

3.3. Secondary Efficacy Endpoints

1. Incidence of HF Hospitalizations or all-cause mortality at 12 months
2. Number of HF Hospitalizations at 6 and 12 months post-implant compared to the number of HF Hospitalizations in the 6 and 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 + #3 at 6 and 12 months post implant
4. Change of N-terminal pro B-type Natriuretic Peptide (NT-proBNP) from Baseline through 6 and 12 months
5. Combined outcome of:
   a. First and recurrent HF Hospitalizations
   b. Heart failure Emergency Department/ Hospital Outpatient IV diuretic visits
   c. all-cause mortality

   at 6 months, added together with equal weighting into a total number of events.
6. Heart failure hospitalization or HF Emergency Department / Hospital Outpatient IV diuretic visits at 6 and 12 month
7. Cardiac and all-cause mortality
8. Days Alive and Out of Hospital (DAOH)
9. Intravenous (IV) diuretic visits
10. Heart failure related Medication changes
11. Change in PAP:
    a. From Baseline through 6 and 12 months in subjects with a baseline mPAP
       i. above target range
       ii. within or below target range
       iii. Overall
    b. Before and after 6-Minute Walk Test
12. Percentage of device success as documented by ability of the System to successfully transmit PAP data
13. Subject Outcome Measures, measured by Kansas City Cardiomyopathy Questionnaire (KCCQ)
14. Functional status improvement, as measured by NYHA and 6-Minute Walk Test
15. Health Economic Analysis (will be covered separately)

3.4. Secondary Safety Endpoints

1. Pressure sensor failure rate throughout the study
2. Frequency of serious adverse events throughout the study
3. Frequency of implant procedure and procedure related adverse events and serious adverse events

4. Analysis Sets

4.1. Enrolled Set

The Enrolled Set will include all subjects enrolled from Cohort #2 and #3. Screen failures are not part of this set. Subjects with either 'Did the Eligibility Committee approve the subject for Implant?' = 'No' (Form: 'Informed Consent') or 'Is subject eligible to participate in this study?' = 'No' (Form 'Eligibility') will be considered as screen failure. For rescreened patients, the previous patient number will be considered as screen failure, and the rescreened patient number will be included in enrolled set. Unless specified otherwise, this set will be used for subject listings and summaries of subject disposition.

4.2. Intent-to-Treat Population

The Intent-to-Treat Population (ITT) will include all enrolled subjects intended to receive the Cordella PA Sensor who entered the Cath Lab, including those in whom Implant Procedure is not attempted for whatever reason (e.g. Cordella PA Sensor Implant cannot be performed due to anatomical reasons) from Cohort #2 and #3. Subjects in this population in whom the Cordella PA Sensor Implant is not attempted will be followed through 30 days for safety purposes. The ITT will be used for all analyses of safety endpoints. Efficacy analysis will not be performed on the ITT population.

4.3. Modified Intent-to-Treat Population (mITT)

The Modified Intent-to-Treat Population (mITT) will include all implanted subjects from Cohort #2 and Cohort #3. All primary and secondary efficacy analyses as well as primary safety analyses will be performed on the mITT.

4.4. Per Protocol Population

The Per Protocol Population (PP) will include all mITT subjects without any major protocol deviations. All primary and secondary safety and efficacy analyses will be performed in addition on PP population. If PP and mITT populations will be identical, analysis will be performed based on mITT only.

4.5. Cohort #1 Population

This population will include all Cohort #1 (previously enrolled Control Arm) implanted subjects and will be reported separately for all applicable tables, figures and listings.

4.6. Comparison Population

This population will include all implanted subjects from Cohort #1, Cohort #2 and #3. The Comparison Population will be used for analysis of secondary efficacy endpoint #3.

4.7. Protocol Deviations

Sponsor will assess the protocol deviations as minor or major and provide this information to Syneos Health prior to date of cut-off, main analysis, and prior to database lock for the follow-up (final) analysis.

5. General Aspects for Statistical Analysis

5.1. General Methods

- Unless otherwise specified, summaries will be presented by cohort (cohort #2 vs cohort #3) and overall
- Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using number of observations (n), frequency and percentages of subjects.
- All relevant subject data will be included in listings. All subjects entered into the database will be included in subject data listings, except screen failures. A separate listing will present the screen failures along with the inclusion criteria they failed and/or exclusion criteria they met. All listings except 16.2.3.x will be repeated for Cohort #1 population.
- In case of multiple assessments at a given time point (planned, repeat, unscheduled) the planned visit will be used for the analysis. For the definition of the baseline value, the last available value (e.g. unscheduled) prior to implant of Cordella PA Sensor will be used.

5.2. Key Definitions

Age

Age at screening is derived in the database and this value will be used for all analyses.

Definition of Baseline for safety assessments

Baseline will be defined as the last available value prior to the implant of Cordella PA Sensor and may be at any visit between Screening (V1) and Cordella PA Sensor Implant Visit (V2).

Definition of Baseline for PAP measurements

Baseline will be defined as value at Implant Visit (V2) obtained before discharge .

Change from Baseline

Absolute change from baseline:
Absolute change = Post-baseline value –baseline value

Time to Onset of AE

Time to onset of AE [days] = Date of start of AE – Date of implant of Cordella PA Sensor + 1

Start Day of concomitant medication

If medication starts before date of implant of Cordella PA Sensor:
Start Day of Medication = Date of start of medication – Date of implant of Cordella PA Sensor
If medication starts at/after date of implant of Cordella PA Sensor
Start Day of Medication = Date of start of medication – Date of implant of Cordella PA Sensor + 1
Incomplete start dates of medication will not be imputed. Start day of medication will be missing.

Stop Day of concomitant medication

If medication stoped before date of implant of Cordella PA Sensor:
Stop Day of Medication = Date of end of medication – Date of implant of Cordella PA Sensor
If medication stops at/after date of implant of Cordella PA Sensor

Stop Day of Medication = Date of end of medication – Date of implant of Cordella PA Sensor + 1
Incomplete end dates of medication will not be imputed. Stop day of medication will be missing.

Definition of study completed/discontinued/ongoing

A subject will be defined as study 'completed'/'discontinued' based on the eCRF information. At the time of the pre-defined main analysis, subjects which are ongoing at date of cut-off will be counted as 'ongoing'.

Time since first diagnosis of heart failure

Time since diagnosis [months] = ((Date of Screening – Date of first HF diagnosis)+1)/30

Exposure time:

which would be exact 6 or 12 months (180 or 365 days respective) post-implant visit for subjects who are still in the study at/after this timepoint.

which would be [date of last available date – date of Implant visit + 1] for subjects who withdraw from study prior to month 6 or 12 (180 or 365 days respective) post-implant visit.

5.3. Missing Data

It is anticipated that there will be little or no missing data that would impact the ability to assess the primary endpoint. The primary efficacy analysis will be based on the mITT population and the primary safety analyses will be based on the population of subjects who underwent a device implant. The primary analysis methods naturally handle missing data by censoring subjects who have dropped out. For the primary safety analyses, the endpoints can be considered as dichotomous and the extreme cases as well as a tipping point analysis can be presented.

For all other analysis, missing data will not be replaced.

5.4. Visit Windows

Every attempt should be made to perform evaluations at the designated time points. However, for visits conducted at Month 1 and 3 there is a window of +/-7 days, for visits at Month 6 there is a window of +/-14 days and after Month 6 (Month 12, 18, 24 and Year 3) there is a window of +/-30 days. All visits will be summarized according to the nominal visit.

5.5. Pooling of Sites

Subjects will be pooled across sites for analysis of study endpoints. Sites with at least 20 subjects will retain their identities. Smaller sites will be ranked in decreasing order of size (site identification numbers, smallest first, will be used to break ties) and cumulatively pooled until pooled sites of no less than 10 subjects are achieved. After this pooling process, it will be tested for homogeneity in the treatment effects across site by using the same poisson model for primary endpoint but to add pooled site as a covariate. The homogeneity test will be conducted at the 0.15 level effect for pooled_site.

```
proc genmod data = xxx;
        class pooled_site;
       model number of events =  pooled_site  /  type3 dist=poisson
              offset=log(exposure_time);
run;
```

In case homogeneity in the rate across sites is not given, an explorative analysis will be performed as post-hoc analysis, to evaluate in a first step what are the differences between the sites which may lead to different rates across sites. The possible factors will be evaluated during this exploratory analysis. In a second step a more complex analysis, e.g. Bayesian hierarchical model of HF event rates across pooled sites which is

essentially treating site as a random effect could be performed. The final decision on the analysis to be performed will be evaluated outside of this SAP. Pooling of sites will be based on the mITT and PP populations.

5.6. Subgroups

Subgroup analysis are planned to be performed by sex (female/male) and heart failure ejection fraction (HFrEF/HFpEF).

Heart failure ejection fraction will be defined based on the echocardiogram parameter: LVEF (%). If LVEF values are <= 40 then it is 'HFrEF', otherwise if LVEF values is >=50 then it is 'HFpEF'. A separate look will be at the LVEF values is > 40 - < 50 as a HFpEF subgroup.

Subgroup analysis is planned for efficacy and safety endpoints, subject disposition, demographics and other baseline characteristics, prior and concomitant medication.

6. Demographic, Other Baseline Characteristics and Medication

6.1. Subject Disposition and Withdrawals

Subject disposition will be summarized by presenting the number and percentage of subjects eligible for the study, number of subjects in each analysis set, subjects completed the Month 6, V5 visit, subjects completed the Month 12, V6 visit, and completed or discontinued from the study together with the primary reason for premature termination, compliance with taking Cordella System daily reading per protocol. Additionally, presentation will be done by site.

Major protocol deviations will be summarized. In addition, a table will be generated summarizing the number of percentage of patients with a protocol deviation due to COVID-19.

Furthermore, the number of subjects excluded from each analysis set will be summarized by reason for exclusion.

Subject status at the study visits described in Appendix 1: Time and Event Schedule will be summarized presenting number of subjects alive, number of subjects with alive status (inpatient hospitalization/out subject), and number of subject with out status (home/rehabilitation centre/other) by visit.

In addition, subject training on Cordella system at implant visit will be presented in a separate table.

All data will be listed.

6.2. Demographic

Demographic (age, gender, race, ethnicity, height, weight, and BMI), heart failure ejection fraction, and smoking history, will be presented in a summary table for mITT, ITT and PP population.

All data will be listed.

6.3. Medical History and Concomitant Diseases

Medical history data will be summarized by category of medical condition for mITT, ITT and PP population. Medical history conditions with ongoing ticked 'No' will be considered as prior diseases, with ongoing ticked 'Yes' as concomitant diseases. In addition, all data will be listed.

Cardiac medical and surgical history data will be summarized by category of cardiac medical and surgical history for mITT, ITT and PP population. In addition, cardiac medical and surgical history will be listed.

6.4. Other Baseline Characteristics

Summary table will be presented for 'Time since first diagnosis of heart failure', 'Type of first heart failure', 'Previous cardiovascular history', and 'Number of hospitalizations in past year for the cardiovascular reasons'

Cardiovascular history data will be summarized by category. In addition, cardiovascular history be listed.

6.5. Medication

All medications will be coded using the WHO Drug Global B3, March 2019.

The number and percentage of subjects taking baseline and concomitant medications will be summarized overall by Anatomical Therapeutical Chemical (ATC) Levels 2 and 3 for mITT, ITT and PP population. All medication will be listed.

6.5.1. Baseline Medication

Medications started prior to the date of implant will be summarized as 'Baseline' medications.

6.5.2. Concomitant Medication

Medications taken at/after the date of implant will be summarized as 'Concomitant' medications.

7. Efficacy

The population used for efficacy analyses will be the mITT. In addition, all efficacy analysis will be analyzed based on PP population and Cohort #1 population. For CEC related endpoints, tables and figures will be repeated using CEC adjudication results

7.1. Primary Efficacy Endpoint and Analysis

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

The information on mortality will be used as collected on the CRF, AE page with AE outcome = 'Death' or Study completion page with primary reason for discontinuation = 'Death'.

The information on HF hospitalizations will be used as collected on the CRF, Hospitalization page, only hospitalizations due to heart failure and stay at least 24 h will be considered as HF related hospitalizations

7.1.1. Main analysis

The mathematical statement of the null and alternative hypothesis is as follows:

H_0: $r_6 \geq PG_6$

H_A: $r_6 < PG_6$

will be used for the goal. The null hypothesis will be rejected if the upper confidence bound for the rate is less than the performance goal, or equivalently, that the corresponding p-value from the hypothesis test is less than 0.025. An observed rate of less than 0.37 and rejection of the null hypothesis indicate that the observed rate is statistically less than the performance goal, indicating clinically acceptable results and study success. Analysis will be based on a Poisson regression approach for the number of events, with the exposure time as an offset term, where r_6 is the 6-month rate of primary endpoint events and PG_6 is the performance goal. A value of 0.43 will be used for the goal.

The test will be based on each subject's total number of events, treatment arm, and exposure time, where a subject's exposure is the time to death, early study discontinuation or 6 months, whichever is smaller.

```
proc genmod data = xxx;
        model number of events =  dummy /*(dummy variable)*/ /  noint type3 dist=poisson
offset=log(exposure_time);
run;
```

All events until day x, which would be exact 6 months (180 days) post-implant visit would be summarized by cohort. The estimated 6 month incidence of HF related hospitalizations (HFH) or all-cause mortality, along with the 2-sided 95% CIs for the estimated will be presented, and p-value from the hypothesis test. The presentation will also include number of HFH, all-cause mortality, total number of both events, and subjects' event rate of HFH or all-cause mortality is calculated as the total number of observed events per subject divided by the (subject's observed exposure time/180) from implant through 6 months, where a subject's exposure is the time to death, early study discontinuation or 6 months (180 days) post implant visit, whichever is the smallest.

7.1.2. Sensitivity analysis

Sensitivity analyses using a negative binomial approach (with the same terms as the poisson model used in the main analysis) to capture within-subject correlation will be performed.

7.1.3. Supplementary analysis

Then main analysis will be repeated based on the PP population and Cohort #1 population. Interpretation of the p-values will be done in descriptive manner only.

In addition, HFH and all-cause mortality from CEC adjudication results will be analysed separately using same method as the main analysis in Section 7.1.1. Secondary Efficacy Endpoints and Analyses

7.1.4. Incidence of HF Hospitalizations or all-cause mortality at 12 months

The mathematical statement of the null and alternative hypothesis for the first secondary efficacy is as follows:

$$H_O: r_{12} \geqslant PG_{12}$$

$$H_A: r_{12} < PG_{12}$$

where r_{12} is the 12 month rate of secondary endpoint events and PG_{12} is the performance goal. A value of 0.70 will be used for the goal. The null hypothesis will be rejected if the upper confidence bound for the rate is less than the performance goal, or equivalently, that the corresponding p-value from the hypothesis test is less than 0.025. An observed value of less than 0.59 and rejection of the null will indicate that the observed rate is statistically less than the performance goal, indicating clinically acceptable results.

Analysis will be based on a Poisson regression approach for the number of events, with the log follow-up time as an offset term. Sensitivity analyses using a negative binomial approach to capture within-subject correlation will be performed.

12 month incidence of HF related hospitalizations (HFH) or all-cause mortality will be analyzed on the mITT, PP and Cohort #1 population in a similar manner to the primary efficacy endpoint.

7.1.5. Number of HF Hospitalizations at 6 and 12 months post-implant compared to the number of HF Hospitalizations in the 6 and 12 months prior to implant

Heart Failure hospitalizations will be summarized by cohort presenting number of subjects without any hospitalizations at 6 and 12 months post-implant visit, number of subjects with any hospitalizations at 6 and 12 months post-implant visit, number of hospitalizations per subject at 6 and 12 months post-implant visit, and mean number of hospitalizations per subjects at 6 and 12 months post-implant visit. Similar presentation will be done based on the CRF information on the number of hospitalizations in the 6 and 12 months prior to implant. 95 % Clopper-Pearson confidence interval (CI) will be provided in addition for the frequencies as applicable. In additional, Wilcoxon rank sum tests will be performed to compare the number of hospitalizations per subject at 12 months post-implant visit with 12 months prior-implant visit, and compare the number of hospitalizations per subject at 6 months post-implant visit with 6 months prior-implant visit.

The 6 and 12 months timepoint is independently of visit information and is calculated as:

All events until day x, which would be exact 6 or 12 months (180 or 365 days respective) post-implant visit would be summarized.

All events happened between day x and implant visit, which is exact 6 or 12 months (-180 or -365 days respective) pre-implant visit.Analysis will be done based on mITT population, PP population, and Cohort #1 population. Prior to the date of cut-off for the main analysis, it will be confirmed, if analysis based on PP population will be required.

7.1.6. Comparison of the number of HF Hospitalizations or Emergency Department/ Hospital Outpatient IV diuretic visits of Cohort #1 and Cohort #2 + Cohort #3 at 6 and 12 month post implant

The rate of mortality and HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits in each cohort at 6 or 12 month is calculated as the total number of observed events in each cohort divided by the (total observed exposure time/180 or 365) in each cohort from implant visit through 6 months or 12 months.

The information on mortality will be used as collected on the CRF, AE page with AE outcome = 'Death' or Study completion page with primary reason for discontinuation = 'Death'. The information on HF hospitalizations will be used as collected on the CRF, Hospitalization page, emergency department/hospital outpatient IV diuretic visits will be used as collected on the CRF, AE page with AEs resulted in = 'Emergency Department (ED) visit'/' Hospitalization'/ 'Urgent, unscheduled outpatient office/ practice' for AE categorized as 'Heart failure'.

The Cohort #1 and Cohort #2 + Cohort #3 subjects will then be compared with respect to rate of events per unit time using poisson regression. The test will be based on each subject's total number of events, treatment arm, and exposure time, where a subject's exposure is the time to death, early study discontinuation or 6 or 12 months, whichever is smaller.

Let λ_1 be the rate of events per 6/12 moth on the Cohort #1 and let λ_2 be the rate of events per 6/12 month on the Cohort #2 + Cohort #3. The null hypothesis is H_0: $\lambda_1 \leq \lambda_2$ and the alternative hypothesis is H_1: $\lambda_1 > \lambda_2$.

The poisson regression calculation provides a one-sided p-value for the null hypothesis that the rate in the Cohort #1 is less than or equal to the rate in the Cohort #2 + Cohort #3.. The resulting p-values will be seen as explanatory.

```
proc genmod data = xxx;
        class trt;
        model number of events = trt/ type3 dist= poisson offset=log(exposure_time);
run;
```

Analysis will be done based on the Comparison population.

7.1.7. Change of NT-proBNP from Baseline through 6 and 12 months

Change of NT-proBNP from baseline through 6 and 12 months will be presented by means of descriptive statistics at all study visits as described in Appendix 1: Time and Event Schedule.

Analysis will be done based on mITT population, PP population, and Cohort #1 population. Prior to the date of cut-off for the main analysis, it will be confirmed, if analysis based on PP population will be required.

7.1.8. Combined outcome of: a. First and recurrent HF Hospitalizations b. HF Emergency Department/ Hospital Outpatient IV diuretic visits c. all-cause mortality at 6 months

Number of total events will be calculated as the sum of the number of HF hospitalizations, HF emergency department/hospital outpatient IV diuretic visits and all-cause mortality. Both first and recurrent events will contribute to the total number. All events will be equal weighting.

This endpoint will be analyzed similarly as the primary endpoint in Section 7.1.1.

Analysis will be done based on mITT population, PP population and Cohort #1 population. Prior to the date of cut-off for the main analysis, it will be confirmed, if analysis based on PP population will be required.

7.1.9. Heart failure hospitalization or HF Emergency Department / Hospital Outpatient IV diuretic visits at 6 and 12 months

Number of total events will be calculated out of number of HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits at 6 and 12 months. First and recurrent events will account to the total number. All events will be equal weighting.

This endpoint will be analyzed similarly as the primary endpoint in Section 7.1.1.

In addition, time to first HF hospitalization/ time to first HF emergency department/hospital outpatient IV diuretic visit in days will be defined as the time from date of Implant visit to the date of the event. In case of no event during the observation period, subject will be censored on the last available date.

Definition of time to first HF hospitalization (days):

In case of event, time to first HF hospitalization = [(Date of event – date of Implant visit) + 1]

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

Definition of time to first HF emergency department/hospital outpatient IV diuretic visit (days):

In case of event, time to first HF emergency department/hospital outpatient IV diuretic visit = [(Date of event – date of Implant visit) + 1]

In case of no event, time to HF emergency department/hospital outpatient IV diuretic visit = [(Date of last available date – date of Implant visit) + 1], this data will be censored.

Median duration of time to first HF hospitalization, time to first HF emergency department/hospital outpatient IV diuretic visit and respective 95% CIs will be reported using Kaplan Meier estimator and Kaplan Meier plot.

```
proc lifetest data = xxx
        time days * censor(1);
run;
```

Time to HF hospitalization and time to HF emergency department/hospital outpatient IV diuretic visit will be listed.

Analysis will be done based on mITT population, PP population, and Cohort #1 population. Prior to the date of cut-off for the main analysis, it will be confirmed, if analysis based on PP population will be required.

7.1.10. Cardiac and all-cause mortality

Time to all-cause mortality in days will be defined as the time from date of Implant visit to the date of the death. In case of no death during the observation period, subject will be censored on the last available date known alive.

Similarly, time to cardiac mortality in days will be defined as the time from date of Implant visit to the date of the cardiac death. In case of no cardiac death during the observation period, subject will be censored on the last available date known without cardiac death event.

Definition of time to death (days):

In case of event, time to death = [(Date of death – date of Implant visit) + 1]

In case of no event, time to death = [(Last available date – date of Implant visit) + 1], this data will be censored.

Definition of time to cardiac death (days):

In case of event, time to cardiac death = [(Date of cardiac death – date of Implant visit) + 1]

In case of no event, time to cardiac death = [(Last available date without cardiac death event – date of Implant visit) + 1], this data will be censored.

Time to death/cardiac death will be listed and summarized by descriptive statistics.

Median duration of time to death and respective 95% CIs will be reported using Kaplan Meier estimator and Kaplan Meier plot.

```
proc lifetest data = xxx
        time days * censor(1);
run;
```

Analysis will be done based on mITT population, PP population, and Cohort #1 population. Prior to the date of cut-off for the main analysis, it will be confirmed, if analysis based on PP population will be required.

7.1.11. Days Alive and Out of Hospital (DAOH)

Days Alive and Out of Hospital (DAOH) calculated by subtracting days in hospital from total exposure time, where a subject's exposure is the time to death, early study discontinuation or 6 or 12 months, respectively, whichever is the smallest will be presented by means of descriptive statistics at 6 and 12 months post-implant visit.

Analysis will be done based on mITT population, PP population, and Cohort #1 population. Prior to the date of cut-off for the main analysis, it will be confirmed, if analysis based on PP population will be required.

7.1.12. Hospital Outpatient IV diuretic visits

This endpoint will be analyzed similarly as the primary endpoint in Section 7.1.1.

Analysis will be done based on mITT population, PP population, and Cohort #1 population. Prior to the date of cut-off for the main analysis, it will be confirmed, if analysis based on PP population will be required.

7.1.13. Heart failure related medication changes

Heart failure related medication change since last visit is collected via eCRF 'Has there been a change in the cardiovascular medication since last visit' and will be summarized by visit presenting the number and percentage of subjects with and without any change in HF medication.

Analysis will be done based on mITT population, PP population, and Cohort #1 population. Prior to the date of cut-off for the main analysis, it will be confirmed, if analysis based on PP population will be required.

7.1.14. Change in PA pressure

Change from baseline in PAP parameters collected via CorPASS: pulmonary artery pressure systolic, pulmonary artery pressure diastolic, pulmonary artery pressure mean and pulse will be presented by treatment group by means of descriptive statistics at before and after 6-minute walk test.

mPAP will be summarized by 'Above target range', 'Within or below target range', and 'Overall' for subjects with a baseline mPAP, at all study visits as described in Appendix 1: Time and Event Schedule including post implant measurement, and sitting vs. supine measurements. Shifts in mPAP from baseline over all post-baseline visits will be presented. Target range of mPAP is 5-20 mmHg. When there are more than one available results collected on same visit, please use the earliest one.

Analysis will be done based on mITT population, and PP population. Prior to the date of cut-off for the main analysis, it will be confirmed, if analysis based on PP population will be required.

7.1.15. Percentage of device success as documented by ability of the System to successfully transmit PAP data

For the analysis of this endpoint, external data, provided by Endotronix, will be used. The provided data will include information if the missing PAP data are due to the System issues.

Following derived parameters will be presented:

- A) Total overall number of days of data collection, defined as the sum of all planned collection days (until end of study for final analysis or date of early discontinuation or date of cut-off or date of V6, Month 12 for the main analysis, whichever is smaller) of all subjects, excluding the days with missing data collection due to the subject's missing data transmission.
- B) Number of days with missing overall successful transmission of the collected data due to the System issues, defined as the sum of all unavailable days due to the System issues (until end of study for final analysis or date of early discontinuation or date of cut-off or date of V6, Month 12 date for the main analysis, whichever is smaller) of all subjects
- Overall device success rate of transmission (%), defined as A-B/A * 100
- Per subject device success rate will be calculated similar to the rules above, based on per subject data only.

Per subject device success rate will be presented by means of descriptive statistics, overall device success rate as percentage, other parameters will be presented using counts.

Presentation will be done overall as all parameters are transmitted together.

Analysis will be done based on mITT population, PP population, and Cohort #1 population. Prior to the date of cut-off for the main analysis, it will be confirmed, if analysis based on PP population will be required.

7.1.16. Subject Outcome Measures, measured by Quality of Life KCCQ questionnaire

The Quality of Life KCCQ questionnaire is a measure of health-related quality of life. Data will be collected at the study visits described in Appendix 1: Time and Event Schedule. For the analysis of this endpoint, external data, provided by Endotronix, will be used.

The KCCQ is a 23-item, refer to Protocol, section 14.4, self-administered instrument that quantifies physical function, symptoms (frequency, severity, and recent change), social function, self-efficacy and knowledge, and quality of life related to HF.

Out of 23-items, 10 scores will be calculated according to the rules in Appendix 2: The Kansas City Cardiomyopathy Questionnaire Scoring Instructions: Physical Limitation, Symptom Stability, Symptom Frequency, Symptom Burden, Total Symptom Score, Self-Efficacy, Quality of Life, Social Limitation, Overall Summary Score, Clinical Summary Score.

Presentation will be done by means of descriptive statistics including the absolute value and change from baseline by visit.

Analysis will be done based on mITT population, PP population, and Cohort #1 population. Prior to the date of cut-off for the main analysis, it will be confirmed, if analysis based on PP population will be required.

7.1.17. Functional status improvement measured by NYHA and 6-Minute Walk Test

NYHA functional classification: The subject's functional status is assessed by a qualified individual at the institution, who is not directly involved with this clinical trial, by utilizing the NYHA functional classification, described in the Protocol Appendix 14.2.

The NYHA functional classification categorizes the extent of heart failure by placing subjects in one of four (I, II, III, IV) categories based on how much they are limited during physical activity and symptoms of shortness of breath and/or angina.

NYHA functional classification will be obtained at all study visits as described in Appendix 1: Time and Event Schedule and must be NYHA Class III for study entry.

Shifts in NYHA functional classification from baseline over all post-baseline visits will be presented.

Six (6) Minute Walk: Subjects complete a six (6) minute walk test at the study visits described in Appendix 1: Time and Event Schedule. Total distance walked (meters) will be collected and analyzed by means of descriptive statistics including the absolute value and change from baseline by visit.

Analysis will be done based on mITT population, PP population, and Cohort #1 population. Prior to the date of cut-off for the main analysis, it will be confirmed, if analysis based on PP population will be required.

8. Safety

The population used for safety analyses will be the ITT. Safety will be assessed on the basis of adverse events (AEs), clinical laboratory data, ECG parameters, Echocardiograms, physical examinations, and vital signs. Primary safety endpoint will be analyzed based on mITT. In addition, AEs will be analyzed based on Cohort #1 population. Primary safety endpoints will also be repeated on ITT, PP population and Cohort #1 population. Secondary safety endpoints will also be analyzed based on PP population and Cohort #1 population. For CEC related endpoints, tables and figures will be repeated using CEC adjudication results

Adverse events and other safety analyses will also be assessed. No formal statistical hypothesis tests will be conducted. Analyses will involve Kaplan-Meier curves for time to event outcomes, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for quantitative outcomes, and count and frequency results for categorical outcomes.

Safety analysis will be performed in first line to address the safety endpoints:

8.1. Primary safety endpoint

8.1.1. Main analysis

There are two primary safety endpoints:

1) Freedom from device/system related complication at 6 months. Freedom from device or system related complications at 6 months will be tested against the null rate of 90%. The endpoint will be assessed based on the AE CRF page with adverse event type = 'Device / System-Related Complication'
2) Freedom from pressure sensor failure at 6 months. Freedom from Pressure Sensor Failure at 6 months will be tested against the null rate of 95%. The endpoint will be assessed based on the AE CRF page with adverse event type = 'Pressure Sensor Failure'

Each of these will be assessed within among all subjects who underwent a device implant by estimating freedom from the event of interest at 6 months by the Kaplan-Meier method.

Definition of time to event (days):

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 or date of day 180 [6 months] – date of Implant visit) + 1], this data will be censored.

The event free rate and respective 95% Cis based on KM method will be compared to the null rate.

For endpoint 1:

H0: rate of freedom from device/system related complication at 6 months <= 90 %

H1: rate of freedom from device/system related complication at 6 months > 90

For endpoint 2:

H0: rate of freedom from pressure sensor failure at 6 months <= 95 %

H1: rate of freedom from pressure sensor failure at 6 months > 95 %

8.1.2. Sensitivity analysis

Two kinds of sensitivity analysis are planned to be performed for the imputation of missing values for the primary safety endpoints. Sensitivity analysis will be performed if the main analysis results show significant effect.

Extreme cases analysis:

In case a subject withdraws from study prior to 6 months follow-up visit and without experiencing previously 'device/system related complication' or 'pressure sensor failure' respectively, the subject will be defined as

having experienced such an event for the 6 months analysis. Setting all missing events to 'Y' would be the only possible extreme cases value. After imputation, below analysis will be performed.

For endpoint 1:
proc freq data= xxx
tables freedom (Y/N) / binomial(exact p=0.90 level = 1) ;
run;
define level = 1 'no event = no device/system related complication'

For endpoint 2:
proc freq data= xxx
tables freedom (Y/N) / binomial(exact p=0.95 level = 1);
run;
define level = 1 'no event = no pressure sensor failure at 6 months'

Tipping point analysis:

If the null hypothesis is rejected for primary safety endpoint, a tipping point analysis will be conducted based on the binary response of freedom from event/with event at 6 months using similar manner as extreme cases analysis. For subjects withdraws from study prior to 6 months follow-up visit and without experiencing previously 'device/system related complication' or 'pressure sensor failure' respectively, setting all missing events to 'N', then gradually increasing the number of subjects with event at 6 months until null hypothesis is not rejected.

8.2. Secondary safety endpoints

1) Pressure sensor failure rate throughout the study
2) Frequency of serious adverse events throughout the study
3) Frequency of implant procedure and procedure related adverse events and serious adverse events

Both secondary endpoints will be evaluated based on the AEs information and covered by AEs outputs.

8.3. Adverse Events

All collected adverse events (AEs) will be coded using MedDRA, version 24.0, to give a preferred term and a SOC term for each event and used for the analysis.

8.3.1.1. *Device deficiency (DD)*

Device deficiency is collected on a separate eCRF page called 'Device deficiency'. Summary will include the number and percent of subjects experienced device deficiency, number and percent of subjects with device deficiency resulted in AE, and number and percent of subjects with potential unanticipated adverse device effect (UADE) due to device deficiency.

8.3.2. Relationship

An AE is considered related, if the relationship to study procedure is documented as 'possibly related', or 'related'.

An AE is considered device/system related complication (DSRC), if the relationship to study device is documented as 'possible related' or 'related'.

An AE is considered related to implant procedure, if the relationship to implant procedure is documented as 'possibly related' or 'related'.

Missing and/or unknown relationship will be presented as separate category, if available.

8.3.3. Predefined AE categories

Following AE categories are predefined in the study protocol, refer to Section 14.6 of the protocol for more information:

1. ACUTE KIDNEY INJURY graded as Stage 1, Stage 2 and Stage 3b
2. BLEEDING graded as Life-threatening or disabling bleeding (BARC type 5 or BARC type 3b and 3c or BARC type 3b), Major bleeding (BARC type 3a), Minor bleeding (BARC type 2 or 3a, depending on the severity)
3. CONDUCTION DISTURBANCES AND ARRHYTHMIAS
4. DEATH classified as Cardiovascular (CV) death, Non-cardiovascular death or undetermined cause of death.
5. DEVICE / SYSTEM-RELATED COMPLICATION
6. HEART FAILURE (HF)
7. HEMOPTYSIS
8. MYOCARDIAL INFARCTION (MI) classified as Peri-procedural MI (≤72 h after the index procedure) or Spontaneous MI (>72 h after the index procedure)
9. PRESSURE SENSOR FAILURE
10. PULMONARY EMBOLISM
11. PULMONARY OCCLUSION
12. RENAL DYSFUNCTION classified as Acute renal dysfunction or Chronic renal dysfunction
13. STROKE (Non-Fatal) AND TRANS ISCHEMIC ATTACK (TIA) classified as Stroke or TIA
    STROKE CLASSIFICATION as Ischemic, Hemorrhagic or undetermined
    STROKE DEFINITION as Disabling stroke or Non-disabling stroke
14. VASCULAR ACCESS SITE AND ACCESS-RELATED COMPLICATIONS classified as Major vascular complications or Minor vascular complications
15. VESSEL TRAUMA classified as Blunt injury or Penetrating injury
16. OTHER <specify>

All SAEs and some selected AEs will be sent for adjudication.

8.3.4. Presentation

Tables will be presented as listed below.

- An overall summary of the number and percentage of subjects reporting AEs, serious AEs, study procedure related AEs, serious study procedure related AEs, AEs leading to withdrawal and AEs leading to death, DSRC, Unanticipated Adverse Device Effect (UADE), implant procedure related AEs, serious implant procedure related AEs, and subjects who died.
- Predefined AEs by category
- AEs, overall and by SOC and preferred term
- Serious AEs, overall and by SOC and preferred term
- Serious AEs, overall and by preferred term
- Serious AEs by Seriousness Criteria
- Serious predefined AEs by category

- Study procedure related AEs, overall and by SOC and preferred term
- Serious study procedure related AEs, overall and by SOC and preferred term
- Implant procedure related AEs, overall and by SOC and preferred term
- Serious implant procedure related AEs, overall and by SOC and preferred term
- Study procedure related AEs by procedure type
- AEs by maximum severity, overall and by SOC and preferred term
- AEs by maximum relationship to implant procedure, overall and by SOC and preferred term
- DSRC, overall and by SOC and preferred term
- DSRC by maximum severity, overall and by SOC and preferred term
- DSRC, by devices
- UADE, overall and by SOC and preferred term
- UADE by maximum severity, overall and by SOC and preferred term
- UADE, by devices
- Implant procedure related AEs, overall and by SOC and preferred term
- Predefined AEs by relationships to device and study procedure from CEC adjudication results
- AEs leading to study withdrawal, overall and by SOC and preferred term
- Device deficiency will be presented as described in Section 8.3.1.1
- AEs, overall and by SOC and preferred term will be done for subjects with predefined AE category 'Pressure Sensor Failure'.
- anticipated AEs, overall and by SOC and preferred term
- anticipated AEs by maximum severity, overall and by SOC and preferred term
- anticipated AEs by maximum relationship to implant procedure, overall and by SOC and preferred term
- unanticipated AEs, overall and by SOC and preferred term
- unanticipated AEs by maximum severity, overall and by SOC and preferred term

- unanticipated AEs by maximum relationship to implant procedure, overall and by SOC and preferred term

- Other serious adverse events (AE) CEC adjudicated by system organ class and preferred term

Listings will be provided for all AEs, UADEs, DSRC, SAEs, anticipated AEs, unanticipated AEs, deaths, AEs leading to study withdrawal and predefined AEs by category. All collected data will be presented as available.

8.4. Laboratory Evaluations

All laboratory analyses will be performed by the local laboratory using standard assay methods. Laboratory evaluation is assessed at the study visits described in Appendix 1: Time and Event Schedule and includes chemistry, hematology, coagulation, Serum NT-pro BNP, and urinalysis with the following parameters:

Chemistry
• Sodium • Potassium • Creatinine • Total bilirubin • Blood urea nitrogen (BUN) • Urea • Total protein • Albumin • CRP • Aspartate aminotransferase (SGOT/AST) • Alanine aminotransferase (SGPT/ALT) • Cholesterol • Uric acid
Hematology
• Hemoglobin • Hematocrit • Leukocytes • Platelets • Lymphocytes
Coagulation
• INR (if indicated) • aPTT
NT-pro BNP
• NT-pro BNP
Urinalysis
• pH • Protein • Glucose • Ketones • Occult blood • RBC • WBC • Urobilinogen

• Bilirubin • Specific gravity • Nitrite
Pregnancy test
• Urine pregnancy test

All laboratory results, including abnormal ranges, will be converted to the International System (SI) units, where applicable.

Summary tables consisting of normal, abnormal clinically significant (CS) and abnormal not clinically significant (NCS) for each parameter, by visit, will be provided. If a parameter has a missing value the result will be included in the summary table as missing.

All data will be included in data listings.

Pregnancy test data will be listed only.

8.5. Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, heart rate, arterial oxygen saturation level (%), weight and BMI) are assessed at all study visits as described in Appendix 1: Time and Event Schedule. For vital signs parameters, absolute values and change from baseline will be presented by means of descriptive statistics at all scheduled study visits.

All data will be included in data listings.

8.6. Electrocardiogram (ECG)

A 12-lead electrocardiogram (ECG) (PR, RR, QRS, uncorrected QT, corrected QTcB, corrected QTcF) is assessed at the study visits described in Appendix 1: Time and Event Schedule. At each scheduled visit Investigator will provide overall ECG evaluation classifying the ECG as normal, abnormal NCS and abnormal CS.

Overall ECG evaluation by visit and shifts from baseline over all post-baseline results will be presented for overall ECG evaluation displaying normal, abnormal NCS and abnormal CS values.

All data will be included in data listings.

8.7. Echocardiogram

Echocardiogram is assessed at the study visits described in Appendix 1: Time and Event Schedule.

Following parameters will be evaluated:

- Left Ventricular Ejection Fraction (%) (LVEF)
- Left ventricular mass
- Left ventricular volume
- Left Ventricular End Diastolic Dimension (LVEDD)
- Left atrial size
- Left atrial volume
- Mitral regurgitation
- Systolic pulmonary artery pressure (sPAP)
- Diastolic pulmonary artery pressure (dPAP)
- Mean pulmonary artery pressure (mPAP)
- Tricuspid regurgitation Peak Velocity
- End Diastolic Pulmonary Regurgitation Gradients

- Right atrial pressure (RAP)
- Overall Interpretation

At each visit Investigator will provide Overall interpretation evaluation classifying the Echocardiogram as normal, abnormal NCS and abnormal CS.

Overall interpretation by visit and shifts from screening to Visit 6 (Month 12) will be presented for overall interpretation displaying normal, abnormal NCS and abnormal CS values.

All data will be included in data listings.

8.8. Physical Examination

Complete physical examinations including body systems: general appearance, dermatological, lymphatic, head/ears/eyes/nose/throat (HEENT), chest/lungs, cardiovascular, abdomen, genitourinary/reproductive, musculoskeletal/extremities, neurologic/psychiatric and other) will be conducted at screening visits, Abbreviated physical examination will be conducted at all study visits as described in Appendix 1: Time and Event Schedule, collecting only the changes from screening assessment.

In addition, chest circumference will be collected at screening.

Physical examination data will be summarized at screening visit, all data will be listed only.

9. Interim Analyses

Interim analysis is not planned.

10. Changes from Analysis Planned in Protocol

During the preparation of the SAP, it was realized that some additional analysis outside the protocol is needed. The respective analysis were introduced in the respective sections and are summarized below.

1) It was clarified that cardiac and all-cause mortality will be analyzed at 6 and 12 months post-implant visit, to be consistent with other efficacy analyses.
2) Two enrollment stopping rules will be considered during the study, both rules will be applied independently of each other and as well independent of the treatment group, see section 2.2. The enrollment stopping rules will ensure enrollment of sufficient number of subjects of certain population: at least 30 % women and at least 45 % HFpEF. This approach was previously confirmed by Sponsor with FDA.
3) Subgroup analysis was not clearly defined in the protocol: two population groups are of interest and were introduced in Section 5.6. This analysis is in line with the introduction of the enrollment stopping rules for the same populations, see Section 2.2.

11. Reference List

1. DSMB Statistical Analysis Plan Version 3.1 dated 07-Feb-2022

2. DSMB charter Version 4.0 dated 04-Mar-2022

3. Abraham, W. T., Adamson, P. B., Bourge, R. C., Aaron, M. F., Costanzo, M. R., Stevenson, L. W., CHAMPION Trial Study Group. (2011). Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomized controlled trial. Lancet, 377, 658-666.

4. Shavelle D. et al. Lower Rates of Heart Failure and All-Cause Hospitalizations During Pulmonary Artery Pressure-Guided Therapy for Ambulatory Heart Failure. Circ Heart Fail. 2020;13:e006863.

5. Angermann, C., Assmus, B., Anker, S.D., Asselbergs, F.W. Pulmonary artery pressureguided therapy in ambulatory patients with symptomatic heart failure: the CardioMEMS European Monitoring Study for Heart Failure (MEMS-HF). Eur J Heart Fail. 2020; 22 (10): 1891-1901

6. PMA P100045/S056B: FDA Summary of Safety and Effectiveness Data (SSED) CardioMEMS™ HF System

7. Lindenfeld, J.A., Zile, M, Desai, A.S., Bhatt, K, Adamson, P. B. Haemodynamic-guided management of heart failure (GUIDE-HF): a randomised controlled trial. Lancet, 2021; 398; 10304: 991-1001

8. PMA P100045 IDE G060187 December 2011 presentation to FDA Circulatory System Devices Advisory Panel. Slide 93-95

12. Programming Considerations

All tables, figures, listings (TFLs), and statistical analyses will be generated using SAS for Windows, Release 9.4 or higher (SAS Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

12.1. General Considerations

- One SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format (RTF). One portable document format pdf will be delivered for tables, listings, and figures.
- Numbering of TFLs will follow ICH E3 guidance

12.2. Table, Listing, and Figure Format

12.2.1. General

- All TFLs will be produced in landscape A4 format, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 9 which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used.
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ).
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

12.2.2. Headers

- All output should have the following header at the top left of each page:
- Endotronix Protocol ETX-HFS-PA-03 (Syneos Health study number 7000235)

- Draft/Final/Follow-up Run
- All output should have Page n of N at the top right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

12.2.3. Display Titles

- Each output is identified by the designation and a numeral (i.e., Table 14.1.1). ICH E3 numbering will be applied. The title is centered. The analysis set is identified on the line immediately following the title.

First Line of Title
Second Line of Title if Needed
(ITT Analysis Set)

12.2.4. Body of the Data Display

12.2.4.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;
- Whole numbers (e.g., counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned.

12.2.4.2. *Table Conventions*

- Units will be included where available
- Unless otherwise specified, only those categories for which there is at least 1 subject represented in 1 or more groups are included.
- Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).
- A Missing category is added to each parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values.
- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Values that round down to 0.0 will be displayed as '<0.1'. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the given

group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

12.2.4.3. *Listing Conventions*

- Listings will be sorted for presentation by subject number, visit/collection day, and visit/collection time.
- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000).
- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

12.2.5. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Subject specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page will be used to display footnotes.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., 'Program: myprogram.sas Listing source: 16.x.y.z').

13. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses.

Syneos Health SOPs Developing Statistical Programming Specifications (3906), Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describe the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

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	14.1.4.3	Baseline medications, stratified by sex	mITT Population
	14.1.4.4	Baseline medications, stratified by heart failure ejection fraction	mITT Population
	14.1.4.5	Baseline medications	Per Protocol Population
	14.1.4.6	Baseline medications	Cohort #1 Population
	14.1.4.7	Concomitant medications	mITT Population
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14.2		Efficacy Data Summary Figures and Tables	
14.2.1		Primary Efficacy Parameter	
	14.2.1.1.1	6-month incidence of HF hospitalizations (HFH) or all-cause mortalities	mITT Population
	14.2.1.1.1a	SAS-Output: 6-month incidence of HF hospitalizations (HFH) or all-cause mortalities	mITT Population
	14.2.1.1.2	6-month incidence of HF hospitalizations (HFH) or all-cause mortalities, stratified by sex	mITT Population
	14.2.1.1.2a	SAS-Output: 6-month incidence of HF hospitalizations (HFH) or all-cause mortalities, stratified by sex	mITT Population
	14.2.1.1.3	6-month incidence of HF hospitalizations (HFH) or all-cause mortalities, stratified by heart failure ejection fraction	mITT Population

Header	Table Number	Name	Analysis Set
	14.2.1.1.3a	SAS-Output: 6-month incidence of HF hospitalizations (HFH) or all-cause mortalities, stratified by heart failure ejection fraction	mITT Population
	14.2.1.1.4	6-month incidence of HF hospitalizations (HFH) or all-cause mortalities	Per Protocol Population
	14.2.1.1.4a	SAS-Output: 6-month incidence of HF hospitalizations (HFH) or all-cause mortalities	Per Protocol Population
	14.2.1.1.5	6-month incidence of HF hospitalizations (HFH) or all-cause mortalities	Cohort #1 Population
	14.2.1.1.5a	SAS-Output: 6-month incidence of HF hospitalizations (HFH) or all-cause mortalities	Cohort #1 Population
	14.2.1.1.6	6-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results	mITT Population
	14.2.1.1.6a	SAS-Output: 6-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results	mITT Population
	14.2.1.1.7	6-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results, stratified by sex	mITT Population
	14.2.1.1.7a	SAS-Output: 6-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results, stratified by sex	mITT Population
	14.2.1.1.8	6-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results, stratified by heart failure ejection fraction	mITT Population
	14.2.1.1.8a	SAS-Output: 6-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results, stratified by heart failure ejection fraction	mITT Population
	14.2.1.1.9	6-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results	Per Protocol Population
	14.2.1.1.9a	SAS-Output: 6-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results	Per Protocol Population
	14.2.1.1.10	6-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results	Cohort #1 Population
	14.2.1.1.10a	SAS-Output: 6-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results	Cohort #1 Population
	14.2.1.1.11	6-month incidence of HF hospitalizations (HFH) from CEC adjudication results	mITT Population
	14.2.1.1.11a	SAS-Output: 6-month incidence of HF hospitalizations (HFH) from CEC adjudication results	mITT Population
	14.2.1.1.12	6-month incidence of all-cause mortalities from CEC adjudication results	mITT Population
	14.2.1.1.12a	SAS-Output: 6-month all-cause mortalities from CEC adjudication results	mITT Population
	14.2.1.2.2	Sensitivity Analysis - 6-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results using negative binomial regression model	mITT Population

Header	Table Number	Name	Analysis Set
	14.2.1.2.2a	SAS-Output: Sensitivity Analysis - 6-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results using negative binomial regression model	mITT Population
14.2.2		Secondary Efficacy Parameters	
14.2.2.1		Incidence of HF Hospitalizations or all-cause mortality at 12 months	
	14.2.2.1.1	12-month incidence of HF hospitalizations (HFH) or all-cause mortalities	mITT Population
	14.2.2.1.1a	SAS-Output: 12-month incidence of HF hospitalizations (HFH) or all-cause mortalities	mITT Population
	14.2.2.1.2	12-month incidence of HF hospitalizations (HFH) or all-cause mortalities, stratified by sex	mITT Population
	14.2.2.1.2a	SAS-Output: 12-month incidence of HF hospitalizations (HFH) or all-cause mortalities, stratified by sex	mITT Population
	14.2.2.1.3	12-month incidence of HF hospitalizations (HFH) or all-cause mortalities, stratified by heart failure ejection fraction	mITT Population
	14.2.2.1.3a	SAS-Output: 12-month incidence of HF hospitalizations (HFH) or all-cause mortalities, stratified by heart failure ejection fraction	mITT Population
	14.2.2.1.4	12-month incidence of HF hospitalizations (HFH) or all-cause mortalities	Per Protocol Population
	14.2.2.1.4a	SAS-Output: 12-month incidence of HF hospitalizations (HFH) or all-cause mortalities	Per Protocol Population
	14.2.2.1.5	12-month incidence of HF hospitalizations (HFH) or all-cause mortalities	Cohort #1 Population
	14.2.2.1.5a	SAS-Output:12-month incidence of HF hospitalizations (HFH) or all-cause mortalities	Cohort #1 Population
	14.2.2.1.6	Sensitivity Analysis - 12-month incidence of HF hospitalizations (HFH) or all-cause mortalities using negative binomial regression model	mITT Population
	14.2.2.1.6a	SAS-Output: Sensitivity Analysis - 12-month incidence of HF hospitalizations (HFH) or all-cause mortalities using negative binomial regression model	mITT Population
	14.2.2.1.7	12-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results	mITT Population
	14.2.2.1.7a	SAS-Output: 12-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results	mITT Population
	14.2.2.1.8	12-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results, stratified by sex	mITT Population
	14.2.2.1.8a	SAS-Output: 12-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results, stratified by sex	mITT Population
	14.2.2.1.9	12-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results, stratified by heart failure ejection fraction	mITT Population

Header	Table Number	Name	Analysis Set
	14.2.2.1.9a	SAS-Output: 12-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results, stratified by heart failure ejection fraction	mITT Population
	14.2.2.1.10	12-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results	Per Protocol Population
	14.2.2.1.10a	SAS-Output: 12-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results	Per Protocol Population
	14.2.2.1.11	12-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results	Cohort #1 Population
	14.2.2.1.11a	SAS-Output:12-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results	Cohort #1 Population
	14.2.2.1.12	Sensitivity Analysis - 12-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results using negative binomial regression model	mITT Population
	14.2.2.1.12a	SAS-Output: Sensitivity Analysis - 12-month incidence of HF hospitalizations (HFH) or all-cause mortalities from CEC adjudication results using negative binomial regression model	mITT Population
14.2.2.2		Number of HF Hospitalizations at 6 and 12 months post-implant compared to the number of HF Hospitalizations in the 6 and 12 months prior to implant	
	14.2.2.2.1	Number of pre and post implant HF hospitalizations at 6 and 12 months post implant visit	mITT Population
	14.2.2.2.2	Number of pre and post implant HF hospitalizations at 6 and 12 months post implant visit, stratified by sex	mITT Population
	14.2.2.2.3	Number of pre and post implant HF hospitalizations at 6 and 12 months post implant visit, stratified by heart failure ejection fraction	mITT Population
	14.2.2.2.4	Number of pre and post implant HF hospitalizations at 6 and 12 months post implant visit	Per Protocol Population
	14.2.2.2.5	Number of pre and post implant HF hospitalizations at 6 and 12 months post implant visit	Cohort #1 Population
	14.2.2.2.6	Number of pre and post implant HF hospitalizations at 6 and 12 months post implant visit from CEC adjudication results	mITT Population
	14.2.2.2.7	Number of pre and post implant HF hospitalizations at 6 and 12 months post implant visit from CEC adjudication results, stratified by sex	mITT Population
	14.2.2.2.8	Number of pre and post implant HF hospitalizations at 6 and 12 months post implant visit from CEC adjudication results, stratified by heart failure ejection fraction	mITT Population
	14.2.2.2.9	Number of pre and post implant HF hospitalizations at 6 and 12 months post implant visit from CEC adjudication results	Per Protocol Population

Header	Table Number	Name	Analysis Set
	14.2.2.2.10	Number of pre and post implant HF hospitalizations at 6 and 12 months post implant visit from CEC adjudication results	Cohort #1 Population
14.2.2.3		Comparison of the number of HF Hospitalizations or Emergency Department/ Hospital Outpatient IV diuretic visits of Cohort #1 and Cohort #2 + Cohort #3 at 6 and 12 months post implant	
	14.2.2.3.1	Comparison of HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits of Cohort #1 and Cohort #2 + Cohort #3 at 6 and 12 months post implant visit	Comparison population
	14.2.2.3.1a	SAS-Output: Comparison of HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits of Cohort #1 and Cohort #2 + Cohort #3 at 6 and 12 months post implant visit	Comparison population
	14.2.2.3.2	Comparison of HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits of Cohort #1 and Cohort #2 + Cohort #3 at 6 and 12 months post implant visit, stratified by sex	Comparison population
	14.2.2.3.2a	SAS-Output: Comparison of HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits of Cohort #1 and Cohort #2 + Cohort #3 at 6 and 12 months post implant visit, stratified by sex	Comparison population
	14.2.2.3.3	Comparison of HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits of Cohort #1 and Cohort #2 + Cohort #3 at 6 and 12 months post implant visit, stratified by heart failure ejection fraction	Comparison population
	14.2.2.3.3a	SAS-Output: Comparison of HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits of Cohort #1 and Cohort #2 + Cohort #3 at 6 and 12 months post implant visit, stratified by heart failure ejection fraction	Comparison population
	14.2.2.3.4	Comparison of HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits of Cohort #1 and Cohort #2 + Cohort #3 at 6 and 12 months post implant visit from CEC adjudication results	Comparison population
	14.2.2.3.4a	SAS-Output: Comparison of HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits of Cohort #1 and Cohort #2 + Cohort #3 at 6 and 12 months post implant visit from CEC adjudication results	Comparison population
	14.2.2.3.5	Comparison of HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits of Cohort #1 and Cohort #2 + Cohort #3 at 6 and 12 months post implant visit from CEC adjudication results, stratified by sex	Comparison population

Header	Table Number	Name	Analysis Set
	14.2.2.3.5a	SAS-Output: Comparison of HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits of Cohort #1 and Cohort #2 + Cohort #3 at 6 and 12 months post implant visit from CEC adjudication results, stratified by sex	Comparison population
	14.2.2.3.6	Comparison of HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits of Cohort #1 and Cohort #2 + Cohort #3 at 6 and 12 months post implant visit from CEC adjudication results, stratified by heart failure ejection fraction	Comparison population
	14.2.2.3.6a	SAS-Output: Comparison of HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits of Cohort #1 and Cohort #2 + Cohort #3 at 6 and 12 months post implant visit from CEC adjudication results, stratified by heart failure ejection fraction	Comparison population
14.2.2.4		Change of N-terminal pro B-type Natriuretic Peptide (NT-pro BNP) from Baseline through 6 and 12 months	
	14.2.2.4.1	NT-proBNP: summary by visit and change from baseline through 12 months	mITT Population
	14.2.2.4.2	NT-proBNP: summary by visit and change from baseline through 12 months, stratified by sex	mITT Population
	14.2.2.4.3	NT-proBNP: summary by visit and change from baseline through 12 months, stratified by heart failure ejection fraction	mITT Population
	14.2.2.4.4	NT-proBNP: summary by visit and change from baseline through 12 months	Per Protocol Population
	14.2.2.4.5	NT-proBNP: summary by visit and change from baseline through 12 months	Cohort #1 Population
14.2.2.5		Combined outcome of a. First and recurrent HF Hospitalizations b. Emergency Department/ Hospital Outpatient IV diuretic visits c. all-cause mortality at 6 months, added together with equal weighting into a total number of events.	
	14.2.2.5.1	Number of events resulted from HF hospitalizations, HF emergency department/hospital outpatient IV diuretic visits and all-cause mortality at 6 months post implant visit	mITT Population
	14.2.2.5.2	Number of events resulted from HF hospitalizations, HF emergency department/hospital outpatient IV diuretic visits and all-cause mortality at 6 months post implant visit, stratified by sex	mITT Population
	14.2.2.5.3	Number of events resulted from HF hospitalizations, HF emergency department/hospital outpatient IV diuretic visits and all-cause mortality at 6 months post implant visit, stratified by heart failure ejection fraction	mITT Population

Header	Table Number	Name	Analysis Set
	14.2.2.5.4	Number of events resulted from HF hospitalizations, HF emergency department/hospital outpatient IV diuretic visits and all-cause mortality at 6 months post implant visit	Per Protocol Population
	14.2.2.5.5	Number of events resulted from HF hospitalizations, HF emergency department/hospital outpatient IV diuretic visits and all-cause mortality at 6 months post implant visit	Cohort #1 Population
	14.2.2.5.6	Number of events resulted from HF hospitalizations, HF emergency department/hospital outpatient IV diuretic visits and all-cause mortality at 6 months post implant visit from CEC adjudication results	mITT Population
	14.2.2.5.7	Number of events resulted from HF hospitalizations, HF emergency department/hospital outpatient IV diuretic visits and all-cause mortality at 6 months post implant visit from CEC adjudication results, stratified by sex	mITT Population
	14.2.2.5.8	Number of events resulted from HF hospitalizations, HF emergency department/hospital outpatient IV diuretic visits and all-cause mortality at 6 months post implant visit from CEC adjudication results, stratified by heart failure ejection fraction	mITT Population
	14.2.2.5.9	Number of events resulted from HF hospitalizations, HF emergency department/hospital outpatient IV diuretic visits and all-cause mortality at 6 months post implant visit from CEC adjudication results	Per Protocol Population
	14.2.2.5.10	Number of events resulted from HF hospitalizations, HF emergency department/hospital outpatient IV diuretic visits and all-cause mortality at 6 months post implant visit from CEC adjudication results	Cohort #1 Population
14.2.2.6		Heart failure hospitalization or Emergency Department / Hospital Outpatient IV diuretic visits at 6 and 12 months	
	14.2.2.6.1	Number of events resulted from HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits at 6 and 12 months post implant visit	mITT Population
	14.2.2.6.2	Number of events resulted from HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits at 6 and 12 months post implant visit, stratified by sex	mITT Population
	14.2.2.6.3	Number of events resulted from HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits at 6 and 12 months post implant visit, stratified by heart failure ejection fraction	mITT Population
	14.2.2.6.4	Number of events resulted from HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits at 6 and 12 months post implant visit	Per Protocol Population
	14.2.2.6.5	Number of events resulted from HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits at 6 and 12 months post implant visit	Cohort #1 Population
	14.2.2.6.6	Time to first heart failure hospitalization: Kaplan-Meier	mITT Population

Header	Table Number	Name	Analysis Set
	14.2.2.6.7	Time to first heart failure hospitalization: Kaplan-Meier, stratified by sex	mITT Population
	14.2.2.6.8	Time to first heart failure hospitalization: Kaplan-Meier, stratified by heart failure ejection fraction	mITT Population
	14.2.2.6.9	Time to first heart failure hospitalization: Kaplan-Meier	Per Protocol Population
	14.2.2.6.10	Time to first heart failure hospitalization: Kaplan-Meier	Cohort #1 Population
	14.2.2.6.11	Time to first heart failure emergency department/hospital outpatient IV diuretic visit: Kaplan-Meier	mITT Population
	14.2.2.6.12	Time to first heart failure emergency department/hospital outpatient IV diuretic visit: Kaplan-Meier, stratified by sex	mITT Population
	14.2.2.6.13	Time to first heart failure emergency department/hospital outpatient IV diuretic visit: Kaplan-Meier, stratified by heart failure ejection fraction	mITT Population
	14.2.2.6.14	Time to first heart failure emergency department/hospital outpatient IV diuretic visit: Kaplan-Meier	Per Protocol Population
	14.2.2.6.15	Time to first heart failure emergency department/hospital outpatient IV diuretic visit: Kaplan-Meier	Cohort #1 Population
	14.2.2.6.26	Number of events resulted from HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits at 6 and 12 months post implant visit from CEC adjudication results	mITT Population
	14.2.2.6.27	Number of events resulted from HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits at 6 and 12 months post implant visit from CEC adjudication results, stratified by sex	mITT Population
	14.2.2.6.28	Number of events resulted from HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits at 6 and 12 months post implant visit from CEC adjudication results, stratified by heart failure ejection fraction	mITT Population
	14.2.2.6.29	Number of events resulted from HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits at 6 and 12 months post implant visit from CEC adjudication results	Per Protocol Population
	14.2.2.6.30	Number of events resulted from HF hospitalizations or HF emergency department/hospital outpatient IV diuretic visits at 6 and 12 months post implant visit from CEC adjudication results	Cohort #1 Population
	14.2.2.6.31	Time to first heart failure hospitalization from CEC adjudication results: Kaplan-Meier	mITT Population
	14.2.2.6.32	Time to first heart failure hospitalization from CEC adjudication results: Kaplan-Meier, stratified by sex	mITT Population
	14.2.2.6.33	Time to first heart failure hospitalization from CEC adjudication results: Kaplan-Meier, stratified by heart failure ejection fraction	mITT Population

Header	Table Number	Name	Analysis Set
	14.2.2.6.34	Time to first heart failure hospitalization from CEC adjudication results: Kaplan-Meier	Per Protocol Population
	14.2.2.6.35	Time to first heart failure hospitalization from CEC adjudication results: Kaplan-Meier	Cohort #1 Population
	14.2.2.6.36	Time to first heart failure emergency department/hospital outpatient IV diuretic visit from CEC adjudication results: Kaplan-Meier	mITT Population
	14.2.2.6.37	Time to first heart failure emergency department/hospital outpatient IV diuretic visit from CEC adjudication results: Kaplan-Meier, stratified by sex	mITT Population
	14.2.2.6.38	Time to first heart failure emergency department/hospital outpatient IV diuretic visit from CEC adjudication results: Kaplan-Meier, stratified by heart failure ejection fraction	mITT Population
	14.2.2.6.39	Time to first heart failure emergency department/hospital outpatient IV diuretic visit from CEC adjudication results: Kaplan-Meier	Per Protocol Population
	14.2.2.6.40	Time to first heart failure emergency department/hospital outpatient IV diuretic visit from CEC adjudication results: Kaplan-Meier	Cohort #1 Population
14.2.2.7		Cardiac and all-cause mortality	
	14.2.2.7.1	Time to cardiac and all-cause mortality: Kaplan-Meier	mITT Population
	14.2.2.7.2	Time to cardiac and all-cause mortality: Kaplan-Meier, stratified by sex	mITT Population
	14.2.2.7.3	Time to cardiac and all-cause mortality: Kaplan-Meier, stratified by heart failure ejection fraction	mITT Population
	14.2.2.7.4	Time to cardiac and all-cause mortality: Kaplan-Meier	Per Protocol Population
	14.2.2.7.5	Time to cardiac and all-cause mortality: Kaplan-Meier	Cohort #1 Population
	14.2.2.7.16	Time to cardiac and all-cause mortality from CEC adjudication results: Kaplan-Meier	mITT Population
	14.2.2.7.17	Time to cardiac and all-cause mortality from CEC adjudication results: Kaplan-Meier, stratified by sex	mITT Population
	14.2.2.7.18	Time to cardiac and all-cause mortality from CEC adjudication results: Kaplan-Meier, stratified by heart failure ejection fraction	mITT Population
	14.2.2.7.19	Time to cardiac and all-cause mortality from CEC adjudication results: Kaplan-Meier	Per Protocol Population
	14.2.2.7.20	Time to cardiac and all-cause mortality from CEC adjudication results: Kaplan-Meier	Cohort #1 Population
14.2.2.8		Days Alive and Out of Hospital (DAOH)	
	14.2.2.8.1	Days alive and out of hospital (DAOH) at 6 and 12 months post implant visit	mITT Population
	14.2.2.8.2	Days alive and out of hospital (DAOH) at 6 and 12 months post implant visit, stratified by sex	mITT Population
	14.2.2.8.3	Days alive and out of hospital (DAOH) at 6 and 12 months post implant visit, stratified by heart failure ejection fraction	mITT Population

Header	Table Number	Name	Analysis Set
	14.2.2.8.4	Days alive and out of hospital (DAOH) at 6 and 12 months post implant visit	Per Protocol Population
	14.2.2.8.5	Days alive and out of hospital (DAOH) at 6 and 12 months post implant visit	Cohort #1 Population
14.2.2.9		Intravenous (IV) diuretic visits	
	14.2.2.9.1	Number of events resulted from hospital outpatient IV diuretic visits at 6 and 12 months post implant visit	mITT Population
	14.2.2.9.2	Number of events resulted from hospital outpatient IV diuretic visits at 6 and 12 months post implant visit, stratified by sex	mITT Population
	14.2.2.9.3	Number of events resulted from hospital outpatient IV diuretic visits at 6 and 12 months post implant visit, stratified by heart failure ejection fraction	mITT Population
	14.2.2.9.4	Number of events resulted from hospital outpatient IV diuretic visits at 6 and 12 months post implant visit	Per Protocol Population
	14.2.2.9.5	Number of events resulted from hospital outpatient IV diuretic visits at 6 and 12 months post implant visit	Cohort #1 Population
	14.2.2.9.6	Number of events resulted from hospital outpatient IV diuretic visits at 6 and 12 months post implant visit from CEC adjudication results	mITT Population
	14.2.2.9.7	Number of events resulted from hospital outpatient IV diuretic visits at 6 and 12 months post implant visit from CEC adjudication results, stratified by sex	mITT Population
	14.2.2.9.8	Number of events resulted from hospital outpatient IV diuretic visits at 6 and 12 months post implant visit from CEC adjudication results, stratified by heart failure ejection fraction	mITT Population
	14.2.2.9.9	Number of events resulted from hospital outpatient IV diuretic visits at 6 and 12 months post implant visit from CEC adjudication results	Per Protocol Population
	14.2.2.9.10	Number of events resulted from hospital outpatient IV diuretic visits at 6 and 12 months post implant visit from CEC adjudication results	Cohort #1 Population
14.2.2.10		Heart failure related medication changes	
	14.2.2.10.1	Heart failure related medication changes by visits	mITT Population
	14.2.2.10.2	Heart failure related medication changes by visits, stratified by sex	mITT Population
	14.2.2.10.3	Heart failure related medication changes by visits, stratified by heart failure ejection fraction	mITT Population
	14.2.2.10.4	Heart failure related medication changes by visits	Per Protocol Population
	14.2.2.10.5	Heart failure related medication changes by visits	Cohort #1 Population
14.2.2.11		Change in PA pressure	
	14.2.2.11.1	Shifts in pulmonary artery pressure mean (mPAP) classification from baseline to post-baseline visits	mITT Population
	14.2.2.11.2	Shifts in pulmonary artery pressure mean (mPAP) classification from baseline to post-baseline visits, stratified by sex	mITT Population

Header	Table Number	Name	Analysis Set
	14.2.2.11.3	Shifts in pulmonary artery pressure mean (mPAP) classification from baseline to post-baseline visits, stratified by heart failure ejection fraction	mITT Population
	14.2.2.11.4	Shifts in pulmonary artery pressure mean (mPAP) classification from baseline to post-baseline visits	Per Protocol Population
	14.2.2.11.5	Comparison between Cordella Sensor PA measurement before and after 6-Minute walk test by visit	mITT Population
	14.2.2.11.6	Comparison between Cordella Sensor PA measurement before and after 6-Minute walk test by visit, stratified by sex	mITT Population
	14.2.2.11.7	Comparison between Cordella Sensor PA measurement before and after 6-Minute walk test by visit, stratified by heart failure ejection fraction	mITT Population
	14.2.2.11.8	Comparison between Cordella Sensor PA measurement before and after 6-Minute walk test by visit	Per Protocol Population
14.2.2.12		Percentage of device success as documented by ability of the System to successfully transmit collected PAP data	
	14.2.2.12.1	Device success rate to transmit collected PAP data	mITT Population
	14.2.2.12.2	Device success rate to transmit collected PAP data	Per Protocol Population
	14.2.2.12.3	Device success rate to transmit collected PAP data	Cohort #1 Population
14.2.2.13		Quality of Life KCCQ questionnaire	
	14.2.2.13.1	Kansas City Cardiomyopathy Questionnaire (KCCQ): Summary for overall and domain scores by visit and change from baseline	mITT Population
	14.2.2.13.2	Kansas City Cardiomyopathy Questionnaire (KCCQ): Summary for overall and domain scores by visit and change from baseline	mITT Population
	14.2.2.13.3	Kansas City Cardiomyopathy Questionnaire (KCCQ): Summary for overall and domain scores by visit and change from baseline	mITT Population
	14.2.2.13.4	Kansas City Cardiomyopathy Questionnaire (KCCQ): Summary for overall and domain scores by visit and change from baseline	Per Protocol Population
	14.2.2.13.5	Kansas City Cardiomyopathy Questionnaire (KCCQ): Summary for overall and domain scores by visit and change from baseline	Cohort #1 Population
14.2.2.14		Functional status improvement	
	14.2.2.14.1	Shifts in NYHA functional classification from baseline to post-baseline visits	mITT Population
	14.2.2.14.2	Shifts in NYHA functional classification from baseline to post-baseline visits, stratified by sex	mITT Population
	14.2.2.14.3	Shifts in NYHA functional classification from baseline to post-baseline visits, stratified by heart failure ejection fraction	mITT Population
	14.2.2.14.4	Shifts in NYHA functional classification from baseline to post-baseline visits	Per Protocol Population

Header	Table Number	Name	Analysis Set
	14.2.2.14.5	Shifts in NYHA functional classification from baseline to post-baseline visits	Cohort #1 Population
	14.2.2.14.6	Six (6)-Minute walk, summary by visit and change from baseline	mITT Population
	14.2.2.14.7	Six (6)-Minute walk, summary by visit and change from baseline, stratified by sex	mITT Population
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17. Appendices

17.1. Appendix 1: Time and Event 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[12]
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	8. Additional RHC as needed for Re-calibration purposes at the clinician's discretion
2. Urine (V1) pregnancy test for females	9. Via CalEQ

3. Echo may be obtained within 3 or 6 months of Screening details are in protocol 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 sitting and supine 7. Additional PAP Measurements will be obtained before and after 6-minute walk test	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 protocol section 8.3.1 16. may be obtained within the 30 day Study Visit 1 window 17. At V9 / Year 3 only

17.2. Appendix 2: The Kansas City Cardiomyopathy Questionnaire Scoring Instructions

Note: references to "**means of questions actually answered**" imply the following.
If there are *n* questions in a scale, and the subject must answer *m* to score the scale, but the subject answers only *n-i*, where *n-i* >= *m*, calculate the **mean of those questions** as (sum of the responses to those *n-i* questions) / (*n-i*)
not
(sum of the responses to those *n-i* questions) / *n*

There are 10 summary scores within the KCCQ, which are calculated as follows:

1. Physical Limitation

Code responses to each of Questions 1a-f as follows:

Extremely limited = 1

Quite a bit limited = 2

Moderately limited = 3

Slightly limited = 4

Not at all limited = 5

Limited for other reasons or did not do = <missing value>

If at least three of Questions 1a-f are not missing, then compute
Physical Limitation Score = 100*[(mean of Questions 1a-f actually answered) – 1]/4

2. Symptom Stability

•Code the response to Question 2 as follows:

Much worse = 1

Slightly worse = 2

Not changed = 3

Slightly better = 4

Much better = 5

I've had no symptoms over the last 2 weeks = 3

If Question 2 is not missing, then compute
Symptom Stability Score = 100*[(Question 2) – 1]/4

3. Symptom Frequency

Code responses to Questions 3, 5, 7 and 9 as follows:

Question 3

Every morning = 1

3 or more times a week but not every day = 2

1-2 times a week = 3

Less than once a week = 4

Never over the past 2 weeks = 5

Questions 5 and 7

All of the time = 1

Several times a day = 2

At least once a day = 3

3 or more times a week but not every day = 4

1-2 times a week = 5

Less than once a week = 6

Never over the past 2 weeks = 7

Question 9

Every night = 1

3 or more times a week but not every day = 2

1-2 times a week = 3

Less than once a week = 4

Never over the past 2 weeks = 5

If at least two of Questions 3, 5, 7 and 9 are not missing, then compute:
S3 = [(Question 3) – 1]/4
S5 = [(Question 5) – 1]/6
S7 = [(Question 7) – 1]/6
S9 = [(Question 9) – 1]/4
Symptom Frequency Score = 100*(mean of S3, S5, S7 and S9)

4. Symptom Burden

Code responses to each of Questions 4, 6 and 8 as follows:

Extremely bothersome = 1

Quite a bit bothersome = 2

Moderately bothersome = 3

Slightly bothersome = 4

Not at all bothersome = 5

I've had no swelling/fatigue/shortness of breath = 5

If at least one of Questions 4, 6 and 8 is not missing, then compute
Symptom Burden Score = 100*[(mean of Questions 4, 6 and 8 actually answered) – 1]/4

5. Total Symptom Score

= mean of the following available summary scores: Symptom Frequency Score and Symptom Burden Score

6. Self-Efficacy

Code responses to Questions 10 and 11 as follows:

Question 10

Not at all sure = 1

Not very sure = 2

Somewhat sure = 3

Mostly sure = 4

Completely sure = 5

Question 11

Do not understand at all = 1

Do not understand very well = 2

Somewhat understand = 3

Mostly understand = 4

Completely understand = 5

If at least one of Questions 10 and 11 is not missing, then compute
Self-Efficacy Score = 100*[(mean of Questions 10 and 11 actually answered) – 1]/4

7. Quality of Life

Code responses to Questions 12, 13 and 14 as follows:

Question 12

It has extremely limited my enjoyment of life = 1

It has limited my enjoyment of life quite a bit = 2

It has moderately limited my enjoyment of life = 3

It has slightly limited my enjoyment of life = 4

It has not limited my enjoyment of life at all = 5

Question 13

Not at all satisfied = 1

Mostly dissatisfied = 2

Somewhat satisfied = 3

Mostly satisfied = 4

Completely satisfied = 5

Question 14

I felt that way all of the time = 1

I felt that way most of the time = 2

I occasionally felt that way = 3

I rarely felt that way = 4

I never felt that way = 5

If at least one of Questions 12, 13 and 14 is not missing, then compute
Quality of Life Score = 100*[(mean of Questions 12, 13 and 14 actually answered) – 1]/4

8. Social Limitation

Code responses to each of Questions 15a-d as follows:

Severely limited = 1

Limited quite a bit = 2

Moderately limited = 3

Slightly limited = 4

Did not limit at all = 5

Does not apply or did not do for other reasons = <missing value>

If at least two of Questions 15a-d are not missing, then compute

Social Limitation Score = 100*[(mean of Questions 15a-d actually answered) – 1]/4

9. Overall Summary Score

= mean of the following available summary scores: Physical Limitation Score, Total Symptom Score, Quality of Life Score, Social Limitation Score

10. Clinical Summary Score

= mean of the following available summary scores: Physical Limitation Score, Total Symptom Score

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