COVERSHEET

The Aortix™ CRS Pilot Study

An Evaluation of the Safety and Performance of the Aortix System for Intra-Aortic Mechanical Circulatory Support in Patients with Cardiorenal Syndrome

Protocol	PVP017
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STATISTICAL ANALYSIS PLAN

TITLE PAGE

The Aortix CRS Pilot Study: An Evaluation of the Safety and Performance of the Aortix System for Intra-Aortic Mechanical Circulatory Support in Patients with Cardiorenal Syndrome (PVP017)

Version 2.0: MAR 23, 2022

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DECLARATION

I, the undersigned, declare that I have prepared the statistical analysis plan along with TLF mockups and that to the best of my knowledge this document is internally consistent with protocol and scientifically rational.

Prepared by:

_____ _____

Name
Designation **Sign & Date (MMM DD, YYYY)**

I, the undersigned declare that I have reviewed the statistical analysis plan along with TLF mockups and that to the best of my knowledge the document is internally consistent with protocol and scientifically rational.

Reviewed by:

_____ _____

Name
Designation **Sign & Date (MMM DD, YYYY)**

AUTHORIZATION: I, the undersigned, declare that I have reviewed the statistical analysis plan along with TLF mock-ups and that to the best of my knowledge the document accurately reflects the protocol objectives.

Authorized by:

_____ _____

Sponsor representative(s) name
Designation **Sign & Date (MMM DD, YYYY)**

REVISION HISTORY

Version	Date	Author	Reasons
1.0	**12 Mar, 2021**	**Mykyta Yakovliev**	**Initial Version.**
2.0	**23 Mar, 2022**	**Mykyta Yakovliev**	**Study analysis algorithms were reviewed based on draft analysis, protocol updates and CRF updates. Main items of interest include analysis of Fluid Intake / Urine Output and analysis of Medications (especially changes in Diuretics in Inotropes doses). Structural changes and additional outputs (including additional figures) were introduced to provide a deeper analysis of the data.**

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACC	American College of Cardiology
ACCF/AHA	American College of Cardiology Foundation / American Heart Association
ACS	Aortix Control System
ADE	Adverse Device Effect
ADHERE	Acute Decompensated Heart Failure National Registry
ADHF	Acute Decompensated Heart Failure
ADS	Aortix Delivery System
AE	Adverse Event
AF	Atrial Fibrillation
AHA	American Heart Association
ARS	Aortix Retrieval System
ASADE	Anticipated Serious Adverse Device Effect
BMI	Body Mass Index
BNP	B-type Natriuretic Peptide
BP	Blood Pressure
BUN	Blood Urea Nitrogen
BSA	Body Surface Area
CAD	Coronary Artery Disease
CBC	Complete Blood Count
CKD	Chronic Kidney Disease
CO	Cardiac Output
COPD	Chronic Obstructive Pulmonary Disease
CPO	Cardiac Power Output
CPT	Current Procedural Terminology
Cr	Creatinine
CRF	Case Report Form

Abbreviation or special term	Explanation
CRRT	Continuous Renal Replacement Therapy
CRS	Cardiorenal Syndrome
CRT	Cardiac Resynchronization Therapy
CVP	Central Venous Pressure
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
EQ5D	the EuroQol-5D, an instrument developed in Europe and widely used, which evaluates the generic quality of life
GCP	Good Clinical Practices
HF	Heart Failure
HFpEF	Heart Failure with a Preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart Rate
IA	Interim Analysis
ICF	Informed Consent Form
ICU	Intensive Care Unit
KCCQ	Kansas City Cardiomyopathy Questionnaire
LDH	Lactate Dehydrogenase
LVAD	Left Ventricular Assist Device
LVEDV	Left Ventricular End-Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVESD	Left Ventricular End-Systolic Dimension
LVESV	Left Ventricular End-Systolic Volume
MAP	Mean Arterial Pressure

Abbreviation or special term	Explanation
NT-pro-BNP	N-terminal pro B-type Natriuretic Peptide
NYHA	New York Heart Association
PA	Pulmonary Artery
PAC	Pulmonary Artery Catheter
PAP	Pulmonary Artery Pressure
PCWP	Pulmonary Capillary Wedge Pressure
PDV	Protocol Deviation
pfH	Plasma Free Hb
QoL	Quality of Life
RR	Respiratory Rate
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SPRAE	Serious Procedure Related Adverse Events
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, Listings, and Figures
USADE	Unanticipated Serious Adverse Device Effect
WRF	Worsening Renal Function

1 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods and data handling methods to be followed during final reporting and any interim analyses of data collected for the study Protocol PVP017.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol Rev G, CRF dated Jan 12, 2022, and Medication Memo dated Mar 9, 2022.

2 STUDY DETAILS

2.1 Study Objectives

The **objectives of the study** are:

- Safety:
  - Observe the nature, severity, and frequency of adverse events associated with the delivery, use, and retrieval of the Aortix Pump.
- Performance:
  - Successfully deliver the Aortix Pump to the descending thoracic aorta using the Aortix Delivery System;
  - Aortix Pump shall function as programmed for the duration of therapy;
  - Manage the Aortix Pump Power Lead and access site over the course of therapy without significant complications;
  - Successfully retrieve and remove the Aortix Pump using the Aortix Retrieval System.
- Effectiveness:
  - Evaluate hemodynamic decongestion (CVP, PCWP) during Aortix therapy;
  - Evaluate the effect of the Aortix therapy on kidney function;
  - Evaluate the impact of the Aortix Pump on clinical biomarkers of congestion.

2.2 Study Design

The study is a prospective, multi-center, non-randomized feasibility study to evaluate the safety and performance of the Aortix System in patients hospitalized with acute decompensated heart failure (ADHF) irrespective of ejection fraction and worsening renal function refractory to medical management with persistent congestion.

2.3 Determination of Sample Size

The sample size of up to thirty (30) implanted patients is based upon industry standards for early stage studies of medical devices; the sample size was not statistically derived.

The study will provide data to be used for demonstrating initial device safety and effectiveness in this patient population, as well as providing input for design of future clinical studies of the device. It is estimated that approximately 50% of patients enrolled may not receive the pump due to anatomical requirements or right heart PA catheterization requirements not being met or inability to implant the pump. Therefore, we plan to enroll up to 60 patients to yield 30 implanted patients.

3 DATA ANALYSIS CONSIDERATION

3.1 General Considerations

The statistical analyses will be performed using SAS Version 9.4 (or higher). All tables, figures and listings will be produced in landscape format.

Data will be presented at each scheduled timepoint (nominal time), where applicable.

The total number of patients in the study group (N) under the stated set of patients will be displayed in the header of summary tables.

All study data will be included in the study data listings. If not stated otherwise listings will be displayed by patient in chronological order.

3.2 General guideline for descriptive summaries

For continuous variables, mean, median, standard deviation, minimum and maximum will be presented for each subgroup and category.

For categorical variables, count and % of patients/counts in each subgroup and/or category will be presented. Percentages will be based on the number of patients with non-missing values, if not specified otherwise.

4 DEFINITION

Baseline, if not specified differently, will be defined as the last non-missing measurement collected during Pre-Implant Period (Baseline Monitoring). For parameters that are not collected during the corresponding time period, the baseline will be defined as the last non-missing measurement prior to Aortix Pump implantation procedure.

TEAEs will be defined as AEs not present prior to the start of study procedures, or AEs present before study treatment that worsened after the implantation procedure. If a partially missing date or time of onset allows the possibility that an AE may be a TEAE it will be assumed that it is a TEAE.

5 STUDY ENDPOINTS

5.1 Primary Safety Endpoints

- Rate of Occurrence of Serious Adverse Events (rate will be calculated and reported) [timeframe: enrollment to 30 day visit];
- Rate of Occurrence of Serious Procedure Related Adverse Events (rate will be calculated and reported) [timeframe: procedure to 30 day visit].

5.2 Device Performance Endpoints

- Deployment and retrieval procedures success rates (rates will be calculated and reported);
- Rate of occurrence of ADS, ARS and pump device-related adverse events (includes device malfunctions) (rate will be calculated and reported) [timeframe: implant attempt/implant to 30 day visit].

5.3 Primary Effectiveness Endpoints

- Clinically significant decongestion as measured by the PA catheter. Decrease in CVP or PCWP of > 20%. [timeframe: pre-implant vs when congestion target is met or therapy deemed ineffective];
- Change in Urine Output Assessed as the hourly rate of urine output before pump implanted vs hourly rate of urine output over the Aortix therapy period until congestion target met or therapy deemed ineffective;
- Decrease in BNP or NT-pro-BNP by 20% (pre-implant vs when congestion target is met or therapy deemed ineffective).

5.4 Additional Data to be Reported

- Rate of occurrence of all adverse events;
- Utilization of continuous renal replacement therapy (CRRT), ultrafiltration and dialysis;
- Change in serum creatinine;

- Change in eGFR;
- Change in diuretic doses;
- Change in urine sodium excretion;
- QoL changes from KCCQ and EQ5D;
- Change in dyspnea assessment;
- Changes in echo parameters (includes CO);
- Changes in cardiac output and cardiac power output;
- Rates of hemolysis as measured by Lactate Dehydrogenase (LDH), Plasma Free Hb (pfH) and urine hemoglobin.

6 ANALYSIS POPULATIONS AND SUBGROUPS

6.1 Analysis Populations

The following populations will be considered for the study:

6.1.1 All Enrolled Population

The All Enrolled population will be defined as all patients who signed the ICF. The All Enrolled population will be used in disposition outputs and/or outputs related to patients' eligibility and partial Safety analysis.

6.1.2 Intent-to-Treat (ITT) Population

The ITT population will be defined as all enrolled patients that have an attempted implant whether or not successful. This population will be used for demographic and partial safety analyses.

6.1.3 As-Treated Population

The As-Treated population will be defined as all enrolled patients with the pump implanted (hemostasis achieved). This population will be used for partial demographic analysis as well as all safety and efficacy analyses.

6.1.4 Pump Speed Changes (PSC) Population

The PSC population will be defined as all enrolled patients with the pump implanted in whom pump speed changes occurred during Aortix Therapy. This population will be used for additional analysis of Laboratory assessments, Vital signs, Hemodynamic parameters and Urine Output measurements.

6.1.5 Diuretic Equivalents Analysis Population

The Diuretic Equivalents Analysis population will be defined as all enrolled patients with the pump implanted who during Baseline and Aortix Treatment analysis periods (see Section 7.4.2) have

received diuretics that are specified in Medication Memo for converting to furosemide equivalents. Patients who during specified analysis periods have not received any diuretics or received diuretics that are not specified in Medication Memo will be excluded. This population will be used for the analysis of furosemide equivalents.

6.2 Subgroups

The following subgroups will be considered for the study based on baseline LVEF (%):

- HFrEF subgroup defined as all patients with LVEF ≤ 45 % at baseline;
- HFpEF subgroup defined as all patients with LVEF > 45 % at baseline.

Unless otherwise specified all summaries will be stratified by the subgroups: HFrEF, HFrEF and Overall.

7 ANALYSIS METHODS

7.1 Disposition

Disposition will be summarized descriptively using counts and percentages for the All Enrolled population by subgroup and overall. The number and percentage of patients screened, screen failures, patients with Aortix Pump implanted and completed the study will be presented, together with number and percentage of patients who prematurely discontinued from the study along with reasons for study discontinuation will be summarized.

A listing of patient's disposition status will be provided. The number of patients in each analysis population will be summarized descriptively with counts and percentages separately. A listing of patient's inclusion to analysis sets will be provided. A patient's eligibility with inclusion/exclusion criteria completions or violations will be listed. Disposition tree plot will be provided associated with corresponding table.

7.2 Demography and Baseline Characteristics

Demographic data and baseline characteristics will include:

- Sex;
- Ethnicity;
- Race;
- Age (years);
- LVEF (%);

- Height (cm);
- Weight (kg);
- Body Mass Index (BMI) (kg/m^2).

Demographics and baseline characteristics will be summarized descriptively by subgroup and overall. Summary statistics including number of patients, mean and standard deviation, median, minimum, and maximum will be generated for all continuous variables such as age, LVEF, height, weight, and BMI. The number and percentage of patients within each category will be presented for all categorical variables such as sex, race, and ethnicity. The summary results will be reported on the ITT and As-Treated populations.

Demographic data and baseline characteristics will be listed for the ITT population with stratification by As-Treated population.

7.3 Medical History

Medical history will be summarized with descriptive statistics by categories for ITT and As-Treated populations by subgroup and overall.

Medical history will be listed for ITT population with stratification based on patient's inclusion into As-Treated population.

7.4 Medications

Summary of medications by category will be provided with descriptive statistics for ITT and As-Treated populations by subgroup and overall.

Doses of Inotropes and Diuretics will be summarized with descriptive statistics for As-Treated population by Timepoint (Baseline Monitoring, Day of Implant, Congestion Target Met, Post 72Hrs or Discharge and Follow-Up).

Listings of medications for ITT population will be provided with stratification based on patient's inclusion into As-Treated population.

7.4.1 Baseline Medications

Baseline medication will be defined as any medication received within 48 hours prior to the start of Aortix treatment. Summary of baseline medications by category will be provided with descriptive statistics for As-Treated populations by subgroup and overall for the following medication categories:

- ACE Inhibitor
- ARNI

- Angiotensin Receptor Blocker
- Beta Blocker
- Diuretic
- Inotrope

In case when start/stop date is incomplete, or medication is ongoing, the following assumption will be made for Baseline medication classification:

- If there is a reasonable possibility that medication was taken within 48 hours prior to the start of Aortix treatment the medication will be considered as Baseline medication;
- If there is no evidence that medication was taken within 48 hours prior to the start of Aortix treatment the medication will not be classified as Baseline medication.

7.4.2 Loop Diuretic – Analysis of Furosemide Equivalents

There will be 2 analysis periods defined:

- Baseline analysis period – from 48 prior to the start of Aortix treatment until the start of Aortix treatment.
- Aortix Treatment analysis period – from the start of Aortix treatment until the end of Aortix treatment.

For the pre-specified list of loop diuretics (which are defined by Medication Memo) an average daily dose of corresponding medication received during the specified analysis period will be derived for the Baseline analysis period and Aortix Treatment analysis period. In cases when start/stop date is incomplete the maximum possible duration of medication treatment will be used for derivation of the average daily dose.

An average daily dose of each specified medication will be converted to furosemide equivalents (per Medication Memo) and the Total Average Daily Dose of Furosemide Equivalents (mg) will be derived as the sum of all converted average daily doses. If there are no diuretics received from a pre-specified list of loop diuretics (which are defined by Medication Memo) during the analysis period (Baseline or Aortix Treatment) then the Total Average Daily Dose of Furosemide Equivalents will be set to 0.

Summary of Total Average Daily Dose of Furosemide Equivalents (mg) at Baseline analysis period and Aortix Treatment analysis period will be provided along with the summary of change from Baseline analysis period to Aortix Treatment analysis period.

Specified derivations and analysis will be conducted only for the Diuretic Equivalents Analysis population.

The list of medications will correspond to the latest version of Medication Memo.

7.4.3 Analysis of Inotropes Dosing Stages

There will be 2 analysis periods defined:

- Baseline analysis period – from 48 prior to the start of Aortix treatment until the start of Aortix treatment.
- Aortix Treatment analysis period – from the start of Aortix treatment until the end of Aortix treatment.

For the pre-specified list of inotropes (which are defined by Medication Memo) an average daily dose of corresponding medication received during the specified analysis period will be derived for the Baseline analysis period and Aortix Treatment analysis period. In cases when start/stop date is incomplete the maximum possible duration of medication treatment will be used for derivation of the average daily dose.

For each analysis period, inotropes will be categorized into stages based on the average daily dose according to the stages table (which is defined by Medication Memo).

Summary of inotropes dosing stages and a proportion of patients with Decreased Stage, Increased Stage and Not Changed will be provided with descriptive statistics by medications category (which are defined by Medication Memo) for As-Treated populations by subgroup and overall.

The list of medications will correspond to the latest version of Medication Memo.

7.5 Protocol Deviations

A listing of protocol deviations will be presented by patient for the All Enrolled population.

7.6 Pump Speed Changes

Pump speed changes will be reported for the PSC population.

7.7 Aortix Pump Deployment/Retrieval Procedure

Aortix Pump Deployment Procedure analysis will include:

- Time from Skin Break to Pump Placement (min)
- Time from Skin Break to delivery Sheath Insertion (min)
- Time from Aortix Pump Final Placement to Hemostasis Achieved (min)
- Questions for Physician Who Performed Aortix Pump Deployment using the ADS
    - Is visibility of system adequate?
    - Is force required to unsheathe Aortix Pump from Delivery Sheath acceptable?

- Is visibility of delivery sheath tip adequate?
- Was overall time to place Aortix Pump acceptable?

Aortix Pump Retrieval Procedure analysis will include:

- Time from Broke Hemostasis at Access Site to Vessel re-access with ARS (min)
- Time from Broke Hemostasis to time Hemostasis Achieved (min)
- Type of Closure Devices used
- Questions for Physician Who Performed Retrieval using the ARS
  - Is visibility of support catheter adequate?
  - Visibility of Retrieval Sheath and Dilator
  - Is force required to re-sheath Aortix Pump acceptable?

Aortix Pump Deployment/Retrieval Procedure parameters will be summarized descriptively by subgroup and overall. Summary statistics including the number of patients, mean and standard deviation, median, minimum, and maximum will be generated for all continuous variables such as Time (min). The number and percentage of patients within each category will be presented for all categorical variables such as Type of Closure Devices used and Questions for Physician Who Performed Retrieval using the ARS. The summary results will be reported based on the As-Treated population.

7.8 Main Study Endpoints

7.8.1 Primary Safety

A Primary Safety analysis will be performed for the As-Treated population to include:

- Percentage of patients with Serious Adverse Events (SAE) defined as the total number of patients with a CEC-classified SAE from the time of enrollment through 30 days post-implant Follow-Up, compared to the total number of patients within the population. Patients with two or more CEC-classified SAE will be counted only once.
- Percentage of patients with Serious Procedure Related Adverse Events (SPRAE) defined as the total number of patients with CEC-classified SPRAE from the time of implant procedure through 30 days post-implant Follow-Up, compared to the total number of patients within the population. Patients with two or more CEC-classified SPRAE will be counted only once. Procedure Related Adverse Events will be defined as any AE related to Aortix Pump Deployment Procedure or Aortix Pump Retrieval Procedure.

Descriptive summaries will be provided for both Percentage of patients with SAE and Percentage of patients with SPRAE for As-Treated population. Corresponding listing will be provided for As-Treated Population.

7.8.2 Device Performance

A Device Performance analysis will be performed for ITT or As-Treated population to include:

- Deployment success defined as total number of patients with a successfully implanted Aortix Pump compared to the total number of patients within ITT population.
- Retrieval success defined as total number of patients with a successfully retrieved Aortix Pump compared to the total number of patients within the As-Treated population.
- Percentage of patients with ADS, ARS and pump device-related adverse events defined as the total number of patients with CEC-classified AEs of the corresponding category from the time of implant procedure through 30 days post-implant Follow-Up compared to the total number of patients in either the ITT population or As-Treated population as appropriate.

Descriptive summary will be provided for variables within Device Performance analysis. Corresponding listing will be provided for ITT population.

7.8.3 Primary Effectiveness

Primary Effectiveness analysis will be performed for As-Treated population to include:

- Percentage of patients with clinically significant decongestion as measured by the PA catheter compared to the total number of patients in the As-Treated population;
- Percentage of patients with a decrease in CVP or PCWP of ≥ 20% from pre-implant until congestion target is met or therapy deemed ineffective compared to the total number of patients in the As-Treated population;
- Change in Urine Output Assessed as the hourly rate of urine output before pump placed vs hourly rate of urine output over the Aortix therapy period until either congestion target met or therapy is deemed ineffective for patients within As-Treated population;
- Percentage of patients with a decrease in BNP or NT-pro-BNP of ≥ 20% from pre-implant until congestion target is met or therapy deemed ineffective with respect to the total number of patients within the As-Treated population.

Descriptive summary of percentages will be provided for device performance analysis variables. Corresponding listings will be provided for As-Treated populations.

In addition, effectiveness measurements (CVP, PCWP, BNP and NT-pro-BNP) collected Day of Implant (Pre-implant) and Once Congestion Target Met will be compared using non-parametric Wilcoxon Signed-Rank by subgroup and overall for those patients within As-Treated populations that have the effectiveness measurements available at both timepoints.

7.8.3.1 Fluid Intake / Urine Output

Cumulative Fluid Intake / Urine Output (mL) will be analyzed starting from the baseline measurement until Aortix retrieval. At each post-implant timepoint cumulative Fluid Intake / Urine Output (mL) will be defined as the total sum across all timepoints until corresponding post-implant timepoint. Cumulative Net Loss (mL) will be defined as the difference between Urine Output and Fluid Intake. Cumulative Fluid Intake, Urine Output and Net Loss will be presented graphically measurement from the baseline until Aortix retrieval by patient for As-Treated and PSC populations.

Hourly rate (mL/h) of Fluid Intake / Urine Output / Net Loss during Aortix therapy will be defined as cumulative Fluid Intake, Urine Output and Net Loss from baseline till the last pre-retrieval timepoint available divided by the number of hours (h) from baseline timepoint measurement till the last pre-retrieval timepoint available.

Baseline hourly rate (mL/h) of Fluid Intake / Urine Output / Net Loss will be defined as of Fluid Intake / Urine Output / Net Loss ([Urine Output] - [Fluid Intake]) from the last pre-baseline measurement to baseline divided by the number of hours (h) from the corresponding last pre-baseline timepoint till baseline.

Hourly rate of Fluid Intake / Urine Output / Net Loss at Baseline, during Aortix therapy and corresponding change from Baseline will summarized with descriptive statistics for As-Treated population.

Boxplots of Hourly rate of Fluid Intake / Urine Output / Net Loss will be provided by subgroup and overall to compare hourly rate during Baseline with hourly rate during Aortix therapy for As-Treated population.

7.9 Safety and Additional Data Analysis

7.9.1 Adverse Events (AE)

CEC classification will be used for the analysis of AEs. Additional overall summary and listing for the Investigator's classification of AEs will be provided.

TEAEs will be defined as AEs not present prior to the start of study procedures, or AEs present before study treatment that worsened after implantation. If a partially missing date or time of onset allows the possibility that an AE may be a TEAE it will be presumed to be a TEAE.

AEs will be summarized by subgroup and overall by the number and percentage of patients who experienced at least one AE of any of the following types: any AE, any TEAE, any TEAE Related to Aortix Therapy, any TEAE Related to Aortix Procedure(Aortix Implant Procedure or Aortix Retrieval Procedure), any TEAE Related to Study Required Procedures, any serious TEAEs, any SAE, any SAE Related to Aortix Procedure, any SAE leading to death, any unanticipated adverse device effect.

AEs will be summarized by categories for the ITT population.

TEAEs will be summarized by category and by relationship for the ITT population.

Listings of all AEs will be provided for the All Enrolled population.

7.9.2 Laboratory assessments

Laboratory measurements will be listed and summarized for actual values and change from baseline with descriptive statistics for As-Treated and PSC populations by Timepoint (Day of Implant, Congestion Target Met, Post 72Hrs or Discharge and Follow-Up). Laboratory measurements will be separated into two categories – Blood Labs and Urine Labs.

Additional summary for lactate dehydrogenase (LDH), plasma free Hb (pfH) and urine hemoglobin will be provided for the As-Treated and PSC populations by Timepoint (Day of Implant, Congestion Target Met, Post 72Hrs or Discharge and Follow-Up).

In addition to the collected laboratory measurements, the following derived parameters will be listed and summarized as the part of Urine Labs category (with the Date/Time of measurement and Timepoint as for corresponding Albumin and Creatinine evaluations):

$$\text{UACR (mg/g)} = \frac{\text{Urine Albumin (mg/dL)}}{\text{Urine Creatinine (g/dL)}}.$$

Laboratory measurements (except for Blood Labs evaluations of Blood Urea Nitrogen and Creatinine) collected from the time of implant until Post 72Hrs or Discharge will be presented graphically by patient for As-Treated and PSC populations.

Blood Labs measurements of Blood Urea Nitrogen and Creatinine collected from the time of implant until Follow-Up will be presented graphically by patient for As-Treated and PSC populations.

Boxplots of Blood Urea Nitrogen and Creatinine will be provided by subgroup and overall to compare baseline results with Congestion Target Met and Follow-Up for As-Treated population.

7.9.3 Vital signs

Vital signs, including measurements of respiratory rate (breathes per minute), heart rate (beats per minute), and BP (mmHg), will be listed and summarized for actual values and change from baseline with descriptive statistics for the As-Treated and PSC populations by Timepoint (Baseline Monitoring, Day of Implant, Congestion Target Met, Post 72Hrs or Discharge and Follow-Up).

Vital signs measurements collected from the time of implant until Post 72Hrs or Discharge will be presented graphically for each patient and each parameter for As-Treated and PSC populations.

7.9.4 Cardiovascular Examination

Cardiovascular examination measurements will be listed and summarized by Timepoint (Pre-Implant, Day of Implant, Congestion Target Met, Day of Retrieval, Post 72Hrs or Discharge and Follow-Up) with descriptive statistics for the As-Treated population by subgroup and overall.

7.9.5 Hemodynamic parameters

Hemodynamic parameters, including measurements of CVP, PCWP, SaO_2, SvO_2 and PA Pressure (Systolic, Diastolic and Mean) will be listed for As-Treated and PSC populations.

Summary of CVP, PCWP and PA Pressure (Systolic, Diastolic and Mean) at Baseline and Once Congestion Target is Met will be provided along with the summary of change from Baseline to Once Congestion Target for As-Treated and PSC populations.

Measurements of CVP, PCWP and PA Pressure (Systolic, Diastolic and Mean) collected starting from the time of implant will be presented graphically for each patient and each parameter for As-Treated and PSC populations.

Boxplots of CVP and PCWP will be provided by subgroup and overall to compare baseline results with Congestion Target Met and Retrieval (defined as the last non-missing measurement collected during Aortix Therapy) for As-Treated population.

7.9.5.1 Cardiac Output and Cardiac Power Output

Cardiac Output (CO) and Cardiac Power Output (CPO) are derived parameters that will be associated with hemodynamic measurements of SaO_2 and SvO_2 (including date and time). Calculations will be based on the last non-missing measurements of Height, Weight, Blood Hemoglobin (BH), Systolic and Diastolic Blood Pressure at Baseline and Once Congestion Target is Met.

Cardiac Output (mL/min) is calculated as:

$$\text{Cardiac Output} = \frac{\text{O}_2\text{consumption}}{\text{Arteriovenous O}_2\text{ difference}} = \frac{125\ \left[\frac{\text{ml O}_2}{\text{min m}^2}\right] * \text{BSA}}{13 *\ \text{BH} * (\text{S}_\text{a}\text{O}_2 -\ \text{S}_\text{v}\text{O}_2)},$$

where Body Surface Area (BSA) is calculated through Haycock's formula:

$$\text{BSA} =\ 0.024265 * (\text{Height [cm]})^{0.3964} * (\text{Weight [kg]})^{0.5378}.$$

Cardiac Power Output (W) is calculated as:

$$\text{Cardiac Power Output} = \frac{\text{Mean Arterial Pressure} * \text{ Cardiac Output}}{451},$$

where Mean Arterial Pressure is calculated by:

$$\text{Mean Arterial Pressure } = \frac{\text{Systolic Blood Pressure} + 2 * \text{Diastolic Blood Pressure}}{3}.$$

Summary of CO and CPO at Baseline and Once Congestion Target is Met will be provided along with summary of change from Baseline to Once Congestion Target for As-Treated and PSC populations.

Detailed listing of CO and CPO will be provided along with all associated measurements for As-Treated and PSC populations .

7.9.6 NYHA

NYHA classification will be listed and summarized by Timepoint with descriptive statistics (counts and percentages) for As-Treated population by subgroup and overall.

7.9.7 Echo parameters

Echo parameters will be listed and summarized by Timepoint with descriptive statistics the for As-Treated population by subgroup and overall.

7.9.8 Dyspnea Evaluation

Dyspnea score evaluation will be listed and summarized by Timepoint (Day of Implant, Congestion Target Met, Day of Retrieval, Post 72Hrs or Discharge and Follow-Up) with descriptive statistics for As-Treated population by subgroup and overall.

Boxplots of dyspnea score will be provided by subgroup and overall to compare baseline results with Congestion Target Met, Post 72Hrs or Discharge and Follow-Up for As-Treated population.

Baseline for dyspnea score will be defined as the last non-missing evaluation prior to Aortix Pump implantation procedure.

7.10 Quality of Life

7.10.1 EQ5D

EQ5D questionnaire will be listed and summarized with descriptive statistics for As-Treated population by subgroup and overall.

Histograms for the proportion of responses by the level of severity for EQ-5D dimensions at baseline and at follow-up will be provided for As-Treated population.

7.10.2 KCCQ

KCCQ questionnaire will be listed for As-Treated population.

KCCQ scores will be summarized with descriptive statistics along with the percentage of patients with increase / decrease of scores by 5 points / up to 25% / from 25% up to 50% / by more than 50% for As-Treated population by subgroup and overall.

Boxplots of Overall Summary Score, Clinical Summary Score and Total Symptom Score will be provided by subgroup and overall to compare baseline results with follow-up for As-Treated population.

7.11 Follow-up Information

Follow-up Information will be listed and summarized with descriptive statistics for As-Treated population by subgroup and overall.

7.12 Deaths

The number of patients who died during the study will be provided along with a vignette discussing the primary cause of death, the temporal course of death and classification for As-Treated population by subgroup and overall.

Only CEC classification of Deaths will be used for analysis.

Listing with detailed information will be provided for the ITT population.

7.13 Interim Analysis

Interim analysis(es) will be conducted in this trial. An interim analysis once 15 patients have been enrolled and/or implanted will be performed. Other ad hoc analyses may be requested.

7.14 Changes to Analyses Specified in Protocol

At the time of this SAP preparation, the following changes have been made to analyses specified in the protocol:

- The protocol specifies analysis of change in Urine Output Assessed as the hourly rate of urine output before pump implanted vs hourly rate of urine output over the Aortix therapy period until congestion target met or therapy deemed ineffective. But timepoint “Once Congestion

Target Met" is not collected in the latest CRF. Due to that, the last pre-retrieval timepoint available is used instead of the Congestion Target Met timepoint.

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